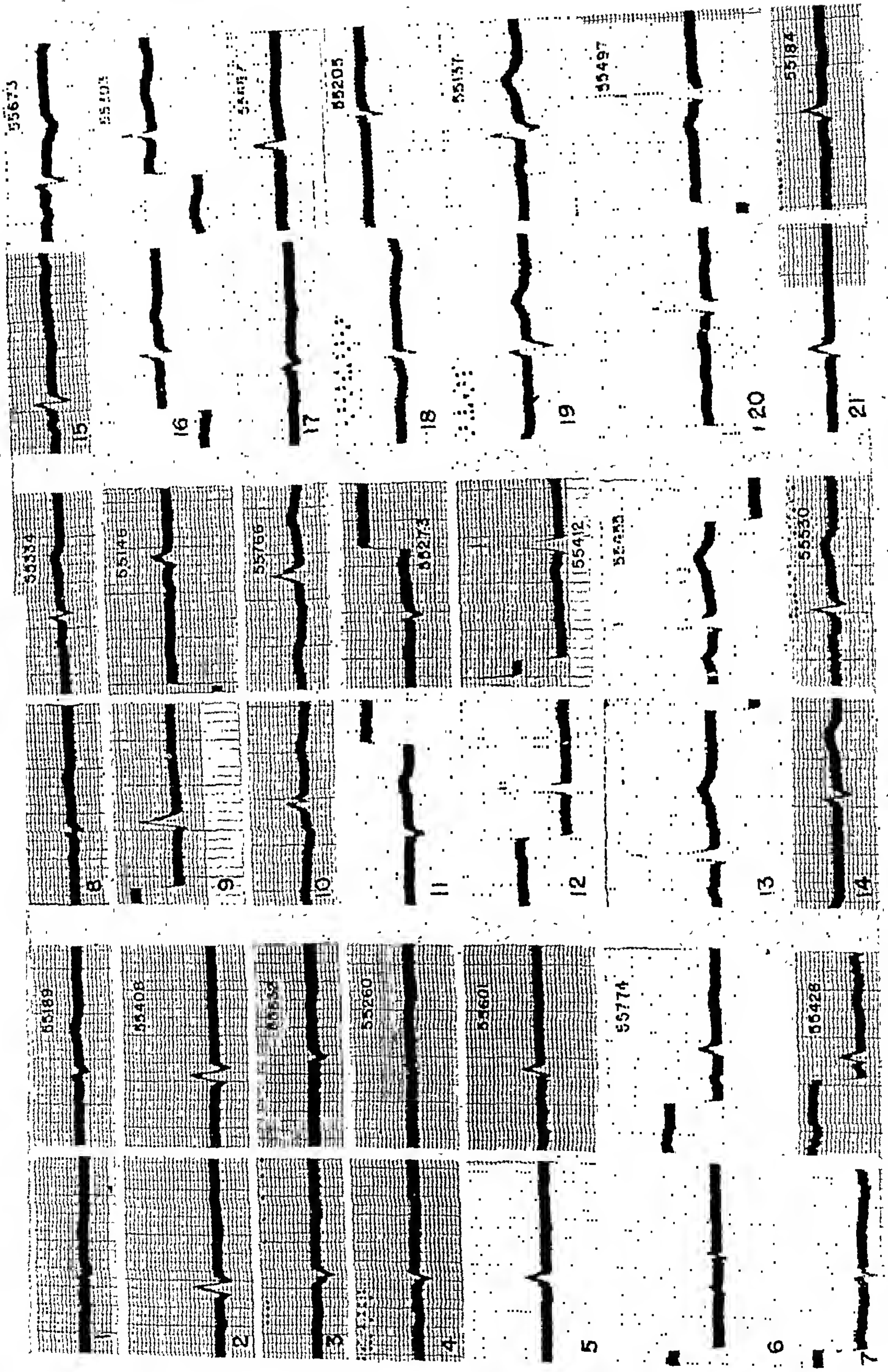

Fig. 1.—Leads from the left arm taken with a central terminal connected to electrodes on the right arm and left leg through resistances of 5,000 ohms. The first tracing of each pair was taken before, the second after, these electrodes were connected together by means of a short length of copper wire.

Of the circuit elements mentioned, the resistances in the arms of the central terminal, at the surfaces of the electrodes, and in the skin are either completely or to a large extent under our control. Making the first as large as is practicable will reduce the currents set up by connecting the limb electrodes to the central terminal to their lowest possible values and thus greatly diminish the likelihood of significant polarization and the magnitude of the alterations in the potential differences inside the body and at its surface produced by this procedure. The limb electrodes should be relatively large also, for the densities of the currents through their surfaces and the underlying skin, and consequently the "contact" and skin resistances and the magnitude of any polarization that may occur, will vary inversely with their size. The skin resistances can be diminished by proper preparation of the skin, and the lower these resistances, the smaller the chance that they will be grossly unequal or constitute large fractions of the total resistances in the circuits of which they are a part.

The simple equations which express the potentials, V_R, V_L, and V_F, of the apices of Einthoven's triangle in terms of the deflections in the standard limb leads were originally based upon the conclusion that the sum of the potentials of these apices is zero for all positions of the electrical axis of the heart. This conclusion may or may not be valid. In either case, these equations give the potentials of the right arm, left arm, and left leg with respect to their mean as the reference level. Take for example the equation for the potential of the left leg in terms of the deflections in Leads II and III.* We have

$$(1) \quad \frac{II + III}{3} = \frac{2V_F - V_R - V_L}{3} = V_F - \left(\frac{V_F + V_R + V_L}{3}\right)$$

The last expression is obtained from the second by first adding and then subtracting V_F.

What exactly do the expressions V_R, V_L, and V_F in these equations represent? That clearly depends upon what the deflections in the limb leads represent. It was shown long ago[4,5] that when the standard limb leads are properly taken one at a time in the usual way, the deflections recorded represent the potential differences between the limb electrodes that would have existed if they had not been attached to the terminals of the electrocardiograph. The principle upon which this surprising conclusion depends is one that was discovered by Helmholtz[6] as long ago as 1853. We conclude, therefore, that the symbols in question represent the potentials of the limb electrodes before they have been brought into contact with any conductor other than the body.

It is then clearly possible to compute the potentials of the limb electrodes with respect to their mean when the deflections in the limb leads are known. The values so obtained may be considered the potentials of these electrodes with respect to an "ideal" central terminal joined to them by infinite resistances. It is also possible, by a procedure analagous to that devised by Einthoven, Bergansius, and Bijtel[4] for another purpose, to construct a central terminal which will have the same potential as an "ideal" terminal of this kind. They showed that by employing three string galvanometers it is possible to take the three limb

leads simultaneously and still obtain accurately standardized records, provided that the resistances in the three circuits are equalized and the sensitivities of the three galvanometers are properly standardized.

We can in the same way adjust the value of the resistances in the three arms of the central terminal in such a way as to make the total resistances in the circuits which include the body equal. The procedure required is the same as that employed by Einthoven and his associates[4] and the example discussed by them is equally suitable for the present purpose. Fig. 2 is reproduced from their paper. The measured body resistances in Leads I, II, and III are given as a, $a + p$, and $a + p + q$, respectively. It is required to determine x, the resistance that must be attached to the right arm electrode, and the resistance y that must be attached to the left arm electrode in order to equalize the resistances in the three limb leads. If we represent the resistances associated with the contacts on the right arm, left arm, and left leg by R_r, R_l, and R_f, respectively, the equalized resistances in three leads will be represented by the following equation:

$$(2) \quad R_r + R_l = a + x + y = R_r + R_f = a + p + x = R_l + R_f = a + p + q + y$$

Solving for x and y, we get x equals $p + q$ and y equals p.

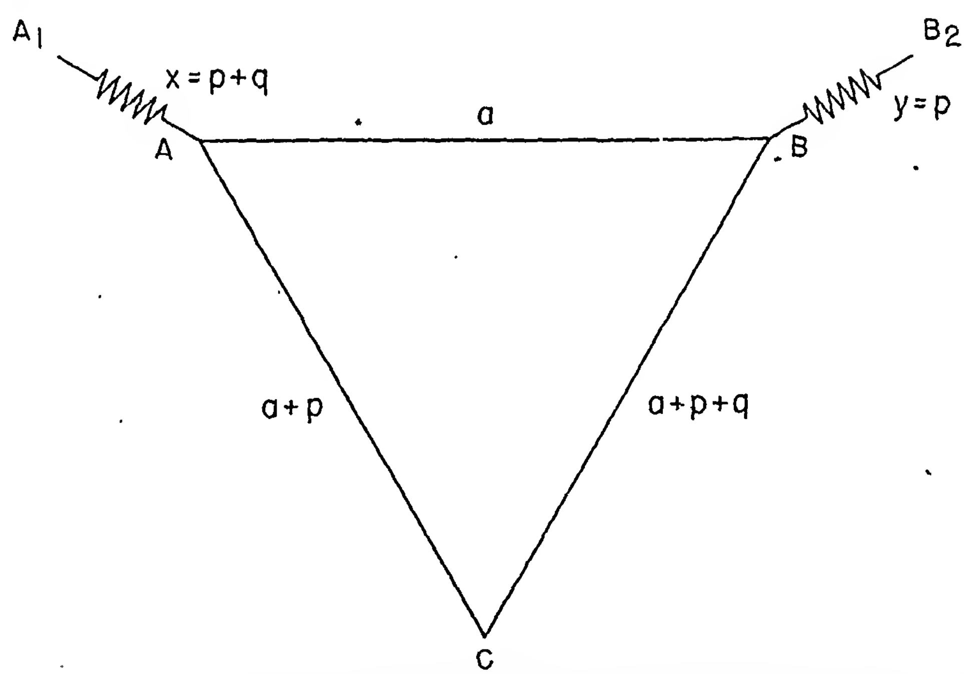

Fig. 2.—Diagram showing method of equalizing the resistances in the limb leads. Reproduced with minor changes from an article by Einthoven, Bergansius, and Bijtel.[4]

A central terminal joined to the right arm electrode (A of Fig. 2) by a resistance R plus x, to the left arm electrode (B) by a resistance R plus y, and to the left leg electrode (C) by a resistance R, will be separated from the points labeled A_1, B_2, and C in Fig. 2 by equal resistances of R ohms. The total resistances in the circuits of which these equal resistances are corresponding elements are equal. Each of the three potential differences between the central terminal and the points A_1, B_2, and C is proportional to, and represents the same fraction

of, the total drop in voltage, or electromotive force, in the circuit to which it belongs. The relations which these statements express are not dependent upon the magnitude of the equal resistances of R ohms. If these resistances are increased step by step, the fraction of the total drop in voltage in each of the circuits corresponding to the potential differences specified will become larger and larger. The limits approached by these potential differences as the value of R becomes infinite are clearly the potentials of the limb electrodes (with respect to their mean) before they were connected to the central terminal. It is easily shown, however, that under the circumstances postulated, the potential of the central terminal is not altered by changing the size of the equal resistors between it and the points A_1, B_2, and C. The sum of the voltage drops across these equal resistors is zero and their relative magnitudes are constant. For very large values of the resistors we have, therefore,

$$(3) \quad (V_R - V_T) + (V_L - V_T) + (V_F - V_T) = O \qquad V_T = \frac{V_R + V_L + V_F}{3}$$

For any other value of the resistors, we have

$$(4) \quad K(V_R - V_T) + K(V_L - V_T) + K(V_F - V_T) = O \qquad V_T = \frac{V_R + V_L + V_F}{3}$$

where K is a fraction equal to R divided by the total resistance in each of the circuits of which the three resistors of R ohms are corresponding elements.

The various circuit elements involved in problems of the kind under consideration are shown diagrammatically in Fig. 3. In this figure E_1, E_2, and E_3

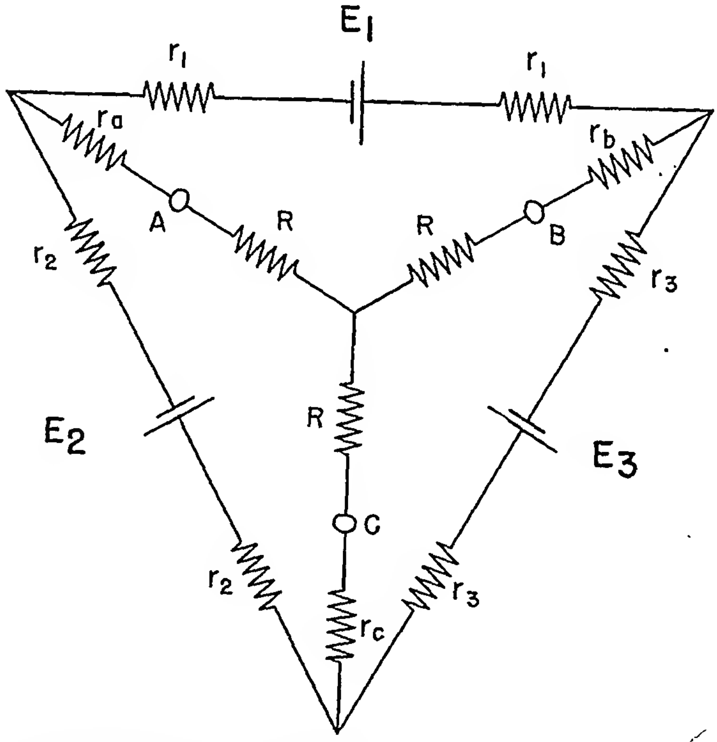

Fig. 3.—Diagram showing the circuit elements of the circuits established by connection of the limb electrodes to a central terminal. See text.

represent the open circuit voltages in the three limb leads, and the small circles (A, B, and C) are the limb electrodes. The body resistances are divided into two fractions. The resistances, across which there is a flow of current only when the limb electrodes are connected one to another by an external conductor, are indicated by the symbols r_a, r_b, and r_c. The other body resistances are labeled r_1, r_2, and r_3. The letter R refers to the equal resistances in the arms of the central terminal. The resistances, r_1, r_2, and r_3, of the tissues of the trunk and those parts of the extremities adjacent to the trunk, through which there is a flow of current before the limb electrodes are joined to any external conductor, are presumably small and approximately equal. On the other hand, the "contact" and skin resistances, which constitute the greater part of r_a, r_b, and r_c, are probably relatively large and frequently unequal.[3]

The following conclusions require no further explanation. When the differences in magnitude between the resistances in the limb leads are small in comparison with R, the potential of the central terminal is the mean of the open circuit potentials of the limb electrodes. When the resistances R are large in comparison with the resistances in the limb leads, the deflections of the leads from the central terminal to the limb electrodes represent the open circuit potentials of these electrodes with respect to their mean. When the resistances R are not large and one of the resistances r_a, r_b, and r_c is much smaller than the other two, the potential of the central terminal will fluctuate in unison with that of the corresponding limb electrode unless the potential variations of this electrode happen to be small in comparison to those of its fellows. When R is not large in comparison with the resistances in the limb leads and r_a, r_b, and r_c are equal, the voltage drops across the resistances R will represent only a fraction of the open circuit potentials of the limb electrodes.

When the value of R is zero, all of the limb electrodes are at the same potential. If the resistances in the limb leads are equal, this potential will be the mean of the open circuit potentials of these electrodes. If r_a, r_b, and r_c are unequal, the potential of the short-circuited limb electrodes will reflect the potential fluctuations of the limb electrode corresponding to the smallest of these resistances. If a central terminal directly connected to the limb electrodes is paired with an exploring electrode, and this electrode is placed on one of the extremities distal to the electrode which is connected to the central terminal, the record obtained will represent the fluctuations of the voltage drop across the skin under the latter. This voltage drop will be proportional to the open circuit potential of the extremity only in case the resistances in the limb leads are precisely equal.

When the resistances R are so large in comparison with the resistances in the limb leads that the voltage drops in the arms of the central terminal are approximately equal to the open circuit potentials of the limb electrodes with respect to their mean, the augmented unipolar limb leads introduced by Goldberger will yield deflections of the same form as, but 50 per cent larger than, the deflections of the corresponding unaugmented leads. This is obviously not the case when R is small, for then the unaugmented leads will record only a small and the augmented leads a large fraction of the open circuit potential variations of the limb

electrodes. When R is zero, the unaugmented leads record nothing. When augmented unipolar leads are taken with a central terminal connected directly to two limb electrodes (R zero), the results are likely to be greatly influenced by the relative magnitude of the two skin resistances involved. The potential of the central terminal, under these circumstances, will not be the mean of the open circuit potentials of the limbs to which it is attached unless these skin resistances are equal.

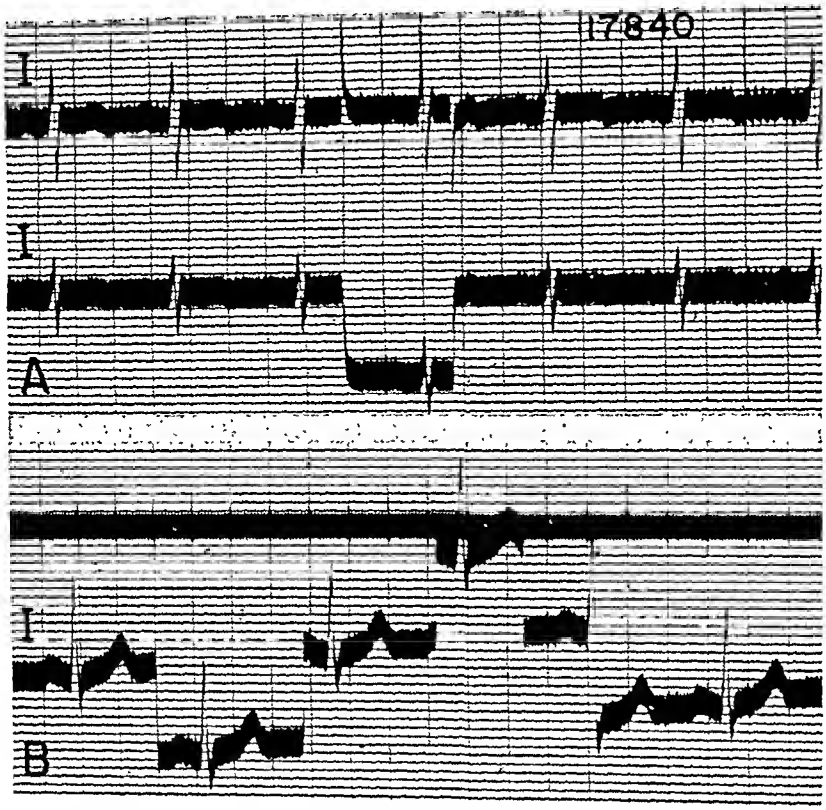

Fig. 4.—*A*, Lead II taken simultaneously with two string galvanometers from a single pair of needle electrodes in the subject's right arm and left leg. The upper record was taken without and the lower record with a single-stage direct current vacuum tube amplifier in the circuit.

B, Record taken with the galvanometer, having the vacuum tube in the circuit, after the other galvanometer had been disconnected from the electrodes.

It may be worth while to give an illustration of the effect on the form of the electrocardiogram produced by polarization in a circuit of relatively low resistance. The tracings shown in Fig. 4 were obtained in the following way. Small steel needles thrust through the skin of the two arms were substituted for the usual limb electrodes and two records of Lead I were taken simultaneously with two coupled string galvanometers. The same electrodes were connected to both galvanometers; to *one* in the usual way and to the other through a single-stage direct current amplifier.[1] The external resistance in the first circuit was then the relatively low resistance of the galvanometer string (about 2,000 ohms), whereas that in the second circuit was the extremely high input resistance of a

vacuum tube. When 1.0 millivolt was thrown into the two circuits, they behaved very differently; the high-resistance circuit yielded a sustained deflection of approximately 1.0 cm. (Fig. 4,*A*). The low-resistance circuit, however, displayed a sharp upward deflection of short duration when the test voltage was thrown in and a similar downward deflection when it was thrown out. On the other hand, the deflections of the two electrocardiographic tracings are identical in form, although different in size. After this record had been taken, the low-resistance circuit was broken and it will be noted that the effect upon the tracing obtained with the high-resistance circuit was profound (Fig. 4,*B*).

We have no evidence bearing on the question as to whether polarization does or does not commonly occur in the low-resistance circuits established when the central terminal is connected directly to the limb electrodes. Nor do we know whether the effects produced by short-circuiting the right arm and left leg electrodes, which are illustrated in Fig. 1, were due chiefly to polarization or chiefly to inequalities of the skin resistances involved. It should be noted that when the standard limb leads are taken with a low-resistance electrocardiograph, the presence of polarization can be easily recognized by the effect which it has upon the deflection produced when a standardizing voltage is thrown into the circuit (Fig. 4). On the other hand, polarization resulting from the flow of current set up by connecting the central terminal to the limb electrodes cannot be easily detected. Polarization arising in this way will distort the tracings obtained through its effect upon the potential of the central terminal; it will not distort the deflection produced by throwing a test voltage into the galvanometer circuit while taking a lead from the central terminal to some other point. It seems essential, therefore, that the resistances in arms of the central terminal be large. Einthoven and Bijtel,[3] who made an exhaustive study of the resistance, electrostatic capacity, and polarization capacity of the skin and their effects upon records taken with the string galvanometer, expressed the opinion that when the external resistance in the galvanometer circuit was 10,000 ohms or more the tracings obtained would not be significantly distorted, provided that the skin resistance had been reduced by the use of 20 per cent sodium chloride solution. At that time the electrodes commonly used were of the immersion type.

CONCLUSIONS

The potential of a central terminal connected to the limb electrodes through resistors of 5,000 ohms and the potential of a central terminal connected directly to these electrodes without intervening resistors may be expected to differ significantly in about one case out of ten.

The resistances in the arms of the central terminal should be large in comparison with the body resistances in the limb leads.

When the resistances in the arms of the central terminal are eliminated, its potential is determined by the relative magnitudes of the resistances of the areas of skin underlying the electrodes to which it is attached and possibly, to some extent, by the effects of polarization.

APPENDIX

A. The Currents in the Arms of the Central Terminal.—

Let i_1, i_2, and i_3 represent the counterclockwise currents in the three loops of the network shown in Fig. 3, containing the resistances r_1, r_2, and r_3, respectively. By Kirchhoff's voltage law we have then the three equations:

$$r_1i_1+R_b(i_1-i_3)+R_a(i_1-i_2)=E_1$$
$$r_2i_2+R_a(i_2-i_1)+R_c(i_2-i_3)=-E_2$$
$$r_3i_3+R_c(i_3-i_2)+R_b(i_3-i_1)=E_3$$

The symbols R_a, R_b, and R_c are here used to represent (r_a+R), (r_b+R), and (r_c+R), respectively. These three equations can be solved for i_1, i_2, and i_3. The expressions for i_a, i_b, and i_c, the currents flowing toward the central terminal through its three branches, may then be computed by means of the relations; i_a equals i_2 minus i_1; i_b equals i_1 minus i_3; and i_c equals i_3 minus i_2.

In this way we obtain

$$i_c=\frac{[r_1r_3+(r_1+r_2+r_3)R_b]E_2+[r_1r_2+(r_1+r_2+r_3)R_a]E_3}{r_1r_2r_3+r_1r_2(R_b+R_c)+r_1r_3(R_a+R_c)+r_2r_3(R_a+R_b)\ (r_1+r_2+r_3)(R_aR_b+R_aR_c+R_bR_c)}$$

For i_a and i_b, the denominator is the same and the numerators are, respectively:

$$-[r_2r_3+(r_1+r_2+r_3)R_c]E_1-[r_1r_3+\ (r_1+r_2+r_3)R_b]E_2 \text{ and}$$
$$[r_2r_3+(r_1+r_2+r_3)R_c]E_1-\ [r_1r_2+(r_1+r_2+r_3)R_a]E_3.$$

When the resistances r_2 and r_3 are equal to r_1, the expression toward the central terminal from the leg electrode is

$$i_c=\frac{(r_1+3R_b)E_2+(r_1+3R_a)E_3}{(r_1)^2+2r_1(R_a+R_b+R_c)+3(R_aR_b+R_aR_c+R_bR_c)}$$

and when, in addition, the resistances R_a and R_b are equal to R_c, we have $i_c=\dfrac{E_2+E_3}{r_1+3R_c}$.

B. The Potential of the Central Terminal.—

When the resistances R_a, R_b, and R_c are equal, the potential of the central terminal is the mean of the potentials of the three extremity electrodes:

$$V_T=(1/3)(V_R+V_L+V_F)$$

When these resistances are unequal, the potential of the central terminal V_T' may be obtained as follows:

We have the equations:

$$(1/R_a)(V_R-V_T')=i_a$$
$$(1/R_b)(V_L-V_T')=i_b$$
$$(1/R_c)(V_F-V_T')=i_c$$

By Kirchhoff's current law the sum of the currents i_a, i_b, and i_c is zero. Consequently,

$$V_T'=\frac{R_bR_cV_R+R_aR_cV_L+R_aR_bR_F}{R_aR_b+R_aR_c+R_bR_c}$$

and

$$V_T'-V_T=\frac{R_bR_cV_R+R_aR_cV_L+R_aR_bV_F}{R_aR_b+R_aR_c+R_bR_c}-\frac{V_R+V_L+V_F}{3}$$

or

$$V_T'-V_T=\frac{R_bR_c(V_R-V_T)+R_aR_c(V_L-V_T)+R_aR_b(V_F-V_T)}{R_aR_b+R_aR_c+R_bR_c}$$

This last equation gives the difference in potential between the central terminal when the resistances are unequal and the central terminal when the resistances are equal in terms of the unequal resistances and the open circuit potentials of the limb electrodes with respect to their mean potential.

When R_b and R_c are equal, but R_a has a different value, we have

$$V'_T - V_T = \frac{R_b(V_R - V_T) + R_a(V_L - V_T) + R_a(V_F - V_T)}{2R_a + R_b}$$

and since $(V_R - V_T) = -(V_L - V_T) - (V_F - V_T)$, this gives

$$V'_T - V_T = \frac{(R_b - R_a)\ (V_R - V_T)}{2R_a + R_b}$$

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NEUTRALIZATION OF THE ANTICOAGULANT EFFECTS OF HEPARIN WITH PROTAMINE (SALMINE)*

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THE anticoagulants, heparin and Dicumarol, are of proved value in the prevention and treatment of intravascular thrombosis. Their advantages and disadvantages have been clearly defined by Allen.[1] One disadvantage common to both is that they may cause bleeding. Bleeding as the result of a Dicumarol-induced prothrombin deficiency may be controlled by the intravenous injection of large doses of vitamin K. Hemorrhage due to a prolonged coagulation time resulting from administration of heparin may be controlled only by discontinuing the administration of heparin or by blood transfusion. These procedures may not prevent the hemorrhage from reaching serious proportions.

Protamines are known to neutralize the effects of heparin both in vitro and in vivo. Protamines appear to have certain toxic effects[2-7] when administered in varying doses to different species of animals. The assumption appears in the literature that because of their toxicity the protamines cannot be safely administered to human subjects. Jorpes and associates,[8] however, said that certain doses of some protamines can be administered to human beings to neutralize the effects of heparin without producing toxic effects. Lam and Cowley[9] have recently stated that protamines may be used to neutralize the effects of heparin on human subjects.

Chargaff and Olson,[3] in 1937, discovered that the anticoagulant effect of heparin in animals was entirely stopped by the intravenous injection of a protamine. They suggested that this method of treatment might be used clinically to interrupt the anticoagulant action of heparin at any time. Jaques, Charles, and Best[4] confirmed the observations of Chargaff and Olson[3] and found that a certain amount of salmine was required to neutralize the effect of a given amount of heparin. Jorpes and co-workers,[8] working in Sweden in 1939, injected a protamine intravenously into human subjects. No undesirable reactions were observed after the intravenous administration of 20 to 75 mg. of a 2 per cent solution of clupeine sulfate to healthy persons, and the anticoagulant effect of heparin was abolished either partially or completely.

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Thompson,[2] in 1900, was the first to show that protamines produced toxic reactions in animals. He found that the intravenous administration of a protamine produced a fall in the arterial blood pressure of dogs. Chargaff and Olson[3] and Jaques, Charles, and Best[4] have shown that protamines are toxic when injected intravenously into dogs. Vartiainen and Marble[5] found that the minimal lethal dose of salmine for rabbits and mice was 200 to 300 mg. per kilogram of body weight when the protamine was administered subcutaneously. Shelley, Hodgkins, and Visscher[6] found that salmine sulfate produced death when administered intravenously to guinea pigs in doses of 6.0 to 12 mg. per 100 grams of body weight. Typical anaphylactoid symptoms occurred before the animals died. Shelley and Tarail[7] injected lethal doses of salmine sulfate into the portal veins of rats and guinea pigs and found that the protamine produced hepatic vascular occlusion.

A search of the literature has disclosed only one article[8] that contains data regarding the intravenous administration of protamines to human subjects. The literature, however, does contain conflicting opinions regarding the administration of protamines to man.

Mason[10] said that protamines are toxic if administered in any form intravenously. Lindgren and Wilander,[11] Leissner,[12] and Ravdin[13] advised the use of protamines for neutralization of heparin in man; however, they provided no data in their reports. Ferguson,[14] in 1946, suggested that toxic reactions caused by overdoses of heparin should be treated with protamine zinc insulin.

EXPERIMENTAL INVESTIGATION

Neutralization of Heparin in Vitro.—We found by in vitro studies that 1.5 mg. of salmine sulfate* neutralized 1.0 mg. of heparin.* A similar ratio was found to exist for 0.5 mg. of heparin because 0.8 mg. of salmine sulfate was required to neutralize this amount of heparin. Protamines exert an anticoagulant effect in vitro. When salmine is present in exactly the amount needed to neutralize heparin, the coagulation time is normal. When heparin or salmine is present in excess in vitro, the coagulation time is prolonged.

Toxicity.—Studies on animals, a complete report of which will be published later, showed that the lethal dose of salmine sulfate when injected intravenously into guinea pigs was 6.0 mg. per 100 grams of body weight. In unanesthetized rabbits, salmine sulfate was injected intravenously in doses as high as 90 mg. per kilogram of body weight without producing severe toxic reactions. In the anesthetized rabbit, salmine sulfate injected intravenously in doses of 10 mg. per kilogram of body weight produced a rapid, transient, moderate fall in arterial blood pressure (Fig. 1,*a*). Intravenous administration of 60 mg. of salmine sulfate per kilogram of body weight to anesthetized rabbits produced death within a short time (Fig. 1,*b*).

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*The heparin used in this study was obtained through the courtesy of the Abbott Laboratories, North Chicago, Ill. The salmine sulfate was obtained through the courtesy of Eli Lilly & Company, Indianapolis, Ind.

Intravenous injection of 1.5 to 2.0 mg. of salmine sulfate per kilogram of body weight into unanesthetized dogs did not produce any toxic effects. Similar injection of 2.0 mg. of salmine sulfate per kilogram of body weight into anesthetized dogs produced a marked transient fall in arterial blood pressure.

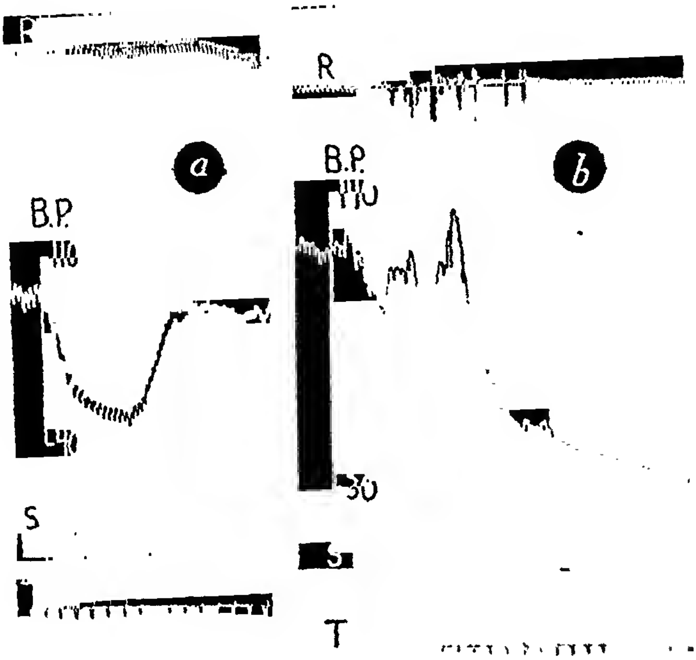

Fig. 1.—*a*, Effect of intravenous injection (at Signal S) of 10 mg. of salmine sulfate per kilogram of body weight on the blood pressure (*B.P.*) and respiration (*R*) of an anesthetized rabbit. (*T* represents the time in intervals of five seconds.)

b, Effect of intravenous injection of 60 mg. of salmine sulfate per kilogram of body weight on the blood pressure of an anesthetized rabbit.

Neutralization of Heparin in Vivo.—After the coagulation time of the blood of three dogs had been determined, 1.0 mg. of heparin per kilogram of body weight was injected intravenously into each animal. The coagulation time of the blood of each animal then was determined at intervals of fifteen minutes until it returned to normal. The intravenous injection of 1.0 mg. of heparin per kilogram of body weight prolonged the coagulation time beyond forty minutes within fifteen minutes after the injection. It was still elevated thirty minutes later but returned to normal within one hour (Fig. 2,*a*). With this to serve as a control, a second series of four dogs received intravenous injections of 1.0 mg. of heparin per kilogram of body weight after the normal coagulation time was determined. Fifteen minutes later, blood was withdrawn for determination of the coagulation time and 1.5 mg. of salmine sulfate per kilogram of body weight was injected intravenously through the same needle. The coagulation time was determined five minutes after the salmine sulfate was injected and at intervals of thirty, forty-five, and sixty minutes after the heparin was injected. In this series of four dogs, the clotting time was elevated beyond fifty minutes, fifteen minutes

after the injection of heparin. After the injection of salmine sulfate, the clotting time rapidly returned to normal within five minutes (Fig. 2,*b*). No toxic reactions were noted in these animals.

In another series of experiments, heparin sodium in Pitkin's menstruum* was administered intramuscularly in doses of 12 mg. per kilogram of body weight to four dogs. The coagulation time was determined at varying intervals for

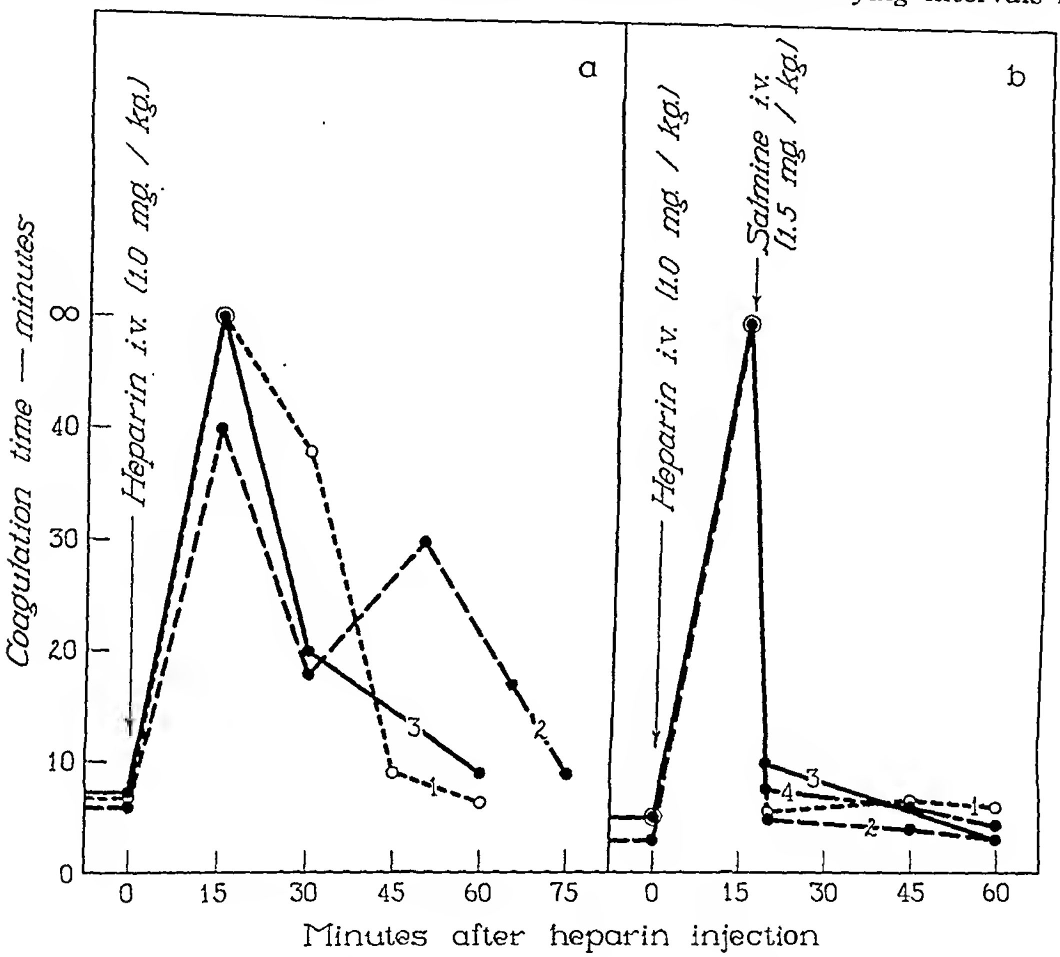

Fig. 2.—*a*, Effect of a single intravenous injection of 1.0 mg. of heparin per kilogram of body weight on the coagulation time of the blood of three dogs.

b, Effect of a single intravenous injection of 1.5 mg. of salmine sulfate per kilogram of body weight on the anticoagulant effect produced by the intravenous administration of 1.0 mg. of heparin per kilogram to each of four dogs.

twenty-four hours after the heparin was administered. The coagulation time was more than fifty minutes for from nine to twelve hours after the injection, but it then gradually returned to normal (Fig. 3,*a*). These results were used as a control. A similar dose of heparin in Pitkin's menstruum then was administered intramuscularly to one dog. The coagulation time was determined two hours after the heparin was administered. One milligram of salmine sulfate per kilogram of body weight was administered intravenously immediately after the

*The Pitkin menstruum was obtained through the courtesy of the Abbott Laboratories. Each cubic centimeter of this menstruum contained 100 mg. of sodium heparin, 180 mg. of gelatin, 80 mg. of dextrose, and 0.01 c.c. of glacial acetic acid in distilled water.

specimen of blood had been withdrawn for the determination of the coagulation time, and a similar dose of salmine was administered intravenously fifteen minutes later. The coagulation time was determined at various intervals for twenty-four hours. The injections of salmine sulfate caused the coagulation time to return nearly to normal for forty-five minutes, but it then became prolonged (Fig. 3,*b*).

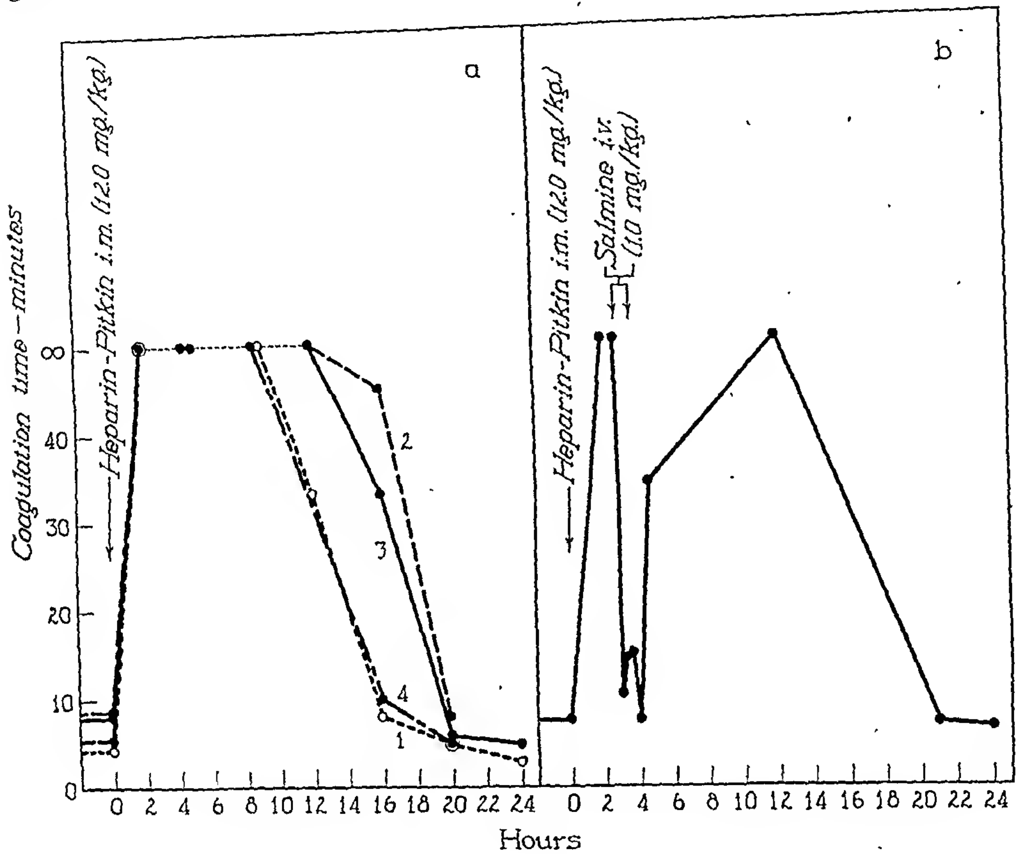

Fig. 3.—*a*, Effect of a single intramuscular injection of 12 mg. of heparin (in Pitkin's menstruum) per kilogram of body weight on the coagulation time of the blood of four dogs.

b, The effect of two intravenous injections of salmine sulfate (each dose 1.0 mg. per kilogram of body weight), given fifteen minutes apart, on the anticoagulant effect produced by the intramuscular administration of one dose of 12 mg. of heparin (in Pitkin's menstruum) per kilogram of body weight to a dog.

CLINICAL OBSERVATIONS

Ten persons kindly consented to undergo certain harmless tests in order that we might determine the amount of salmine sulfate required to neutralize the effects produced by a specific amount of heparin.

Attempts were made to standardize several factors known to influence the coagulation of blood. All equipment was cleansed thoroughly each time it was used. Needles were kept sharp. Trauma upon entering the vein was kept at a minimum. All coagulation times were determined by the Lee-White method. One milliliter of venous blood was placed in a test tube of 8.0 mm. bore that had been rinsed with physiologic salt solution. The tube was tilted at intervals of

thirty seconds until blood no longer flowed in it. All test tubes were kept in an aluminum rack which was placed in a water bath (37°C.) with thermostat temperature control.

For purposes of control, we determined the anticoagulant effect produced by the intravenous administration of 50 mg. of heparin. The coagulation time of the blood of four of the ten persons was determined before the injection, and fifteen, forty-five, and sixty minutes after the injection of heparin. The average normal coagulation time was four minutes and fifteen seconds. At fifteen minutes after the injection of heparin, the average coagulation time was eighteen minutes and fifty-five seconds, at forty-five minutes it was seventeen minutes and twenty-two seconds, and at sixty minutes it was seventeen minutes and sixty-five seconds.

The average coagulation time of the blood of five other persons was determined before 50 mg. of heparin was administered intravenously and at intervals of one, two, and three hours after the heparin was administered. The average normal coagulation time of the blood of these five persons was four minutes and eighteen seconds. At one hour after injection of the heparin the average coagulation time was seventeen minutes and twenty seconds, at two hours it was ten minutes and four seconds, and at three hours it was five minutes and thirty-two seconds. The intravenous administration of 50 mg. of heparin increased the coagulation time to about four times normal for one hour. The coagulation time then decreased gradually and became normal within three hours.

The following plan was used in all cases in which salmine sulfate was administered. After the normal coagulation time was determined, 50 mg. of heparin was administered intravenously. The coagulation time then was determined at intervals of fifteen, thirty, forty-five, sixty, 120, and 180 minutes. Fifteen minutes after the heparin was administered, salmine sulfate was injected intravenously through the same needle that was used to withdraw blood for determination of the coagulation time. Since a period of ten minutes was required for the injection of the salmine sulfate, the blood that was withdrawn for determination of the coagulation time thirty minutes after the administration of heparin actually was withdrawn only five minutes after the completion of the injection of the salmine sulfate.

Neutralization of 50 mg. of Heparin in Man.—A series of ten persons received 50 mg. of heparin intravenously. Fifteen minutes after the injection of heparin, salmine sulfate was administered intravenously to all of the ten persons in doses ranging from 15 to 50 milligrams. When administered in doses of 15 and 25 mg., salmine sulfate was not effective in returning the coagulation time to normal. In cases in which 40 to 50 mg. of salmine sulfate was administered, the coagulation time returned to its normal level within five minutes after the injection of the salmine sulfate and remained there for three hours, during which the coagulation time was determined (Figs. 4 and 5).

No toxic manifestations were noted during or after the administration of salmine sulfate to the human subjects used in the study. No subjective or objective changes appeared. There were no changes in blood pressure, pulse rate, or respiratory rate.

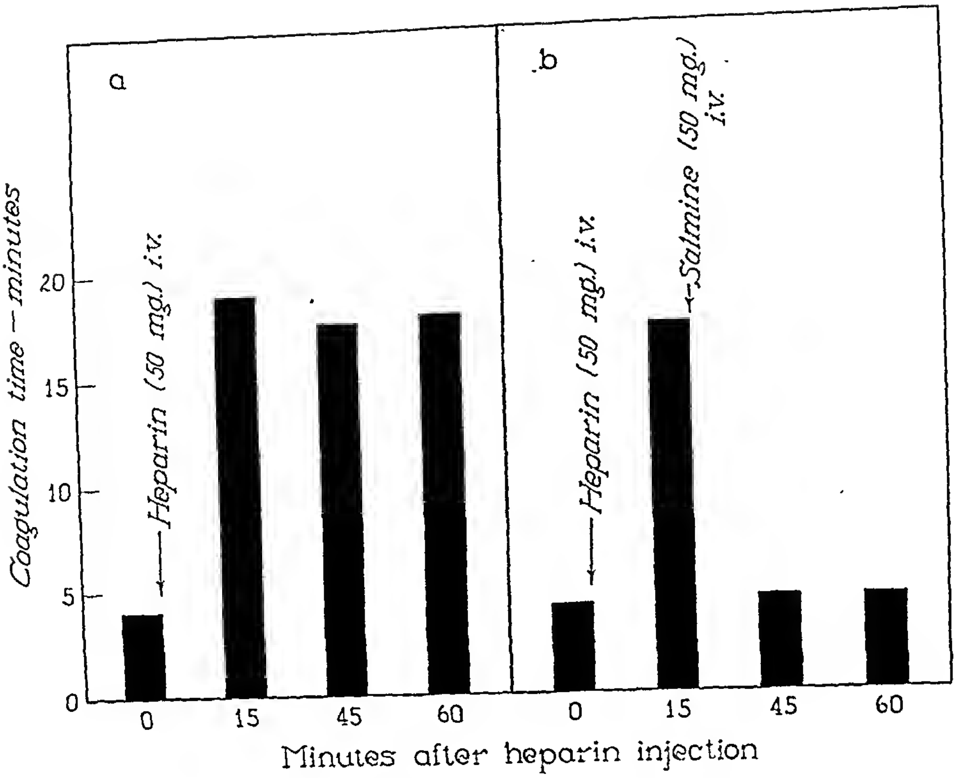

Fig. 4.—*a*, Average effect of a single intravenous injection of 50 mg. of heparin on the coagulation time of the blood of four persons. Coagulation time determined at intervals of fifteen minutes for one hour.

b, Average effect of a single intravenous injection of 50 mg. of salmine sulfate on the anticoagulant effect produced by the intravenous administration of 50 mg. of heparin to four persons. The salmine was injected fifteen minutes after the injection of heparin. Coagulation times were determined at intervals of fifteen minutes for one hour.

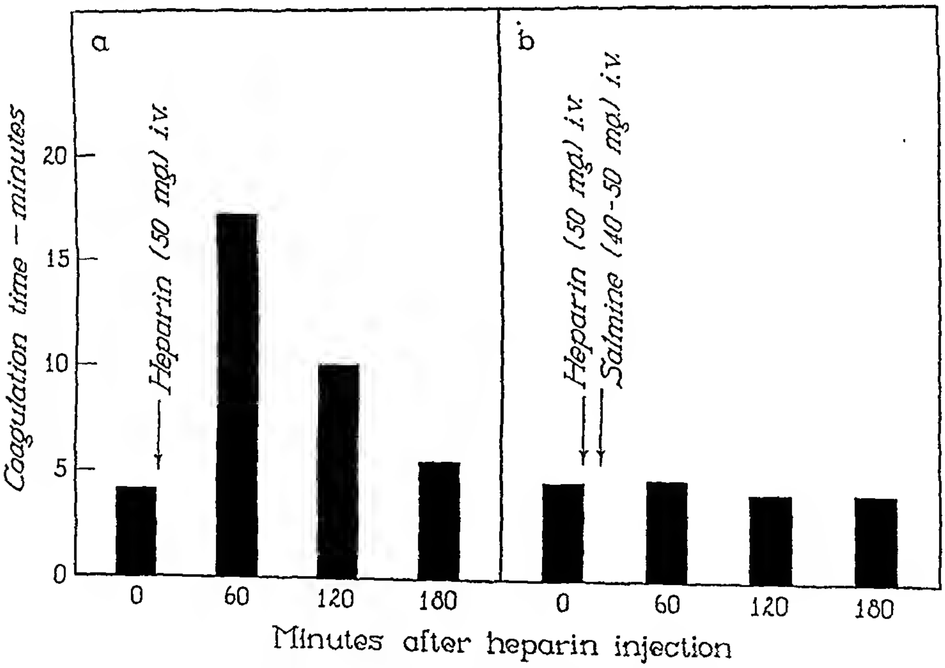

Fig. 5.—*a*, Average effect of a single intravenous injection of 50 mg. of heparin on the coagulation time of the blood of five persons. Coagulation time determined at intervals of one hour for three hours.

b, Average effect of intravenous injection of 40 to 50 mg. of salmine sulfate on the anticoagulant effect produced by the intravenous injection of 50 mg. of heparin to five persons. The salmine sulfate was injected fifteen minutes after the injection of heparin. Coagulation times were determined at intervals of one hour for three hours.

COMMENT

A quantitative relationship was found to exist between salmine sulfate and heparin when titration studies were made in vitro. One and one-half milligrams of salmine sulfate was required to neutralize 1.0 mg. of heparin. This ratio is not the same as that reported by Jaques and his co-workers[4]; however, they used different preparations of heparin and protamine. Varying ratios probably will be obtained when different preparations are used. In addition, the type of blood used for the titration studies should be considered when comparisons are made. Dog blood was used in our in vitro experiments.

The ratio between the amount of salmine sulfate required to neutralize a definite amount of heparin in man appeared to be about 1:1 when fifteen minutes had elapsed between the injection of heparin and the injection of salmine sulfate. If more time would elapse after the injection of heparin, proportionately less heparin would be present in the blood and, consequently, less salmine sulfate should be needed for neutralization.

The thrombocytes, leucocytes, fibrinogen, and prothrombin were not studied during our observations. Chargaff and Olson[3] stated that the hematocrit reading, the thrombocyte count, the concentration of hemoglobin, and the erythrocyte count were not altered in dogs after the intravenous injection of protamine. Thompson[2] stated that there was a decrease in the number of leucocytes in the dogs he studied after intravenous injection of protamines. Mylon, Winternitz, and De Sütö-Nagy[15] reported that protamine precipitates fibrinogen.

It is the consensus of authors[16-19] that protamines are nonantigenic. The report of Walther and Ammon[20] is in disagreement with this view. However, the shock dose they used was so large that a toxic reaction to histamine, independent of an antibody-antigen reaction, may have been the cause of death.

Fifty milligrams of heparin injected intravenously every four hours is the standard dose used in most parts of this country in the prevention and treatment of vascular thromboembolic emergencies. Consequently, no attempt was made to neutralize larger doses of heparin injected by the intermittent intravenous method.

It was observed, however, that salmine sulfate temporarily neutralized heparin which had been incorporated in Pitkin's menstruum and injected intramuscularly into dogs. The neutralizing effect of one intravenous injection of salmine sulfate was of short duration; that is, it lasted about fifteen minutes. Two intravenous injections of salmine sulfate, given fifteen minutes apart, caused the coagulation time to return rapidly to normal and to remain at a normal level for forty-five minutes (Fig. 3,*a* and *b*). In view of these findings, it seems likely that repeated or continuous intravenous injections of small doses of salmine sulfate may be used as an effective means of controlling the effects of heparin which has been incorporated in a delaying menstruum and administered subcutaneously or intramuscularly to human subjects.

Several theoretical problems deserve some consideration in a study of this kind. Does the possibility exist that a sudden reduction of an elevated blood

coagulation time to normal initiates vascular thrombosis? In the present study no clinical evidence of thrombosis was observed after the intravenous injection of salmine sulfate. Another consideration is whether the blood will become hypercoagulable when more salmine sulfate is injected intravenously than is required for neutralization of heparin. It has been demonstrated by Jaques[21] and also in this study that there is a quantitative neutralization of heparin and that if an excess of salmine sulfate exists in the blood in vitro an anticoagulant effect is produced. In vivo, no anticoagulant effect due to protamines was observed with doses which produced no toxic manifestations. In vitro, protamines do exert an anticoagulant effect on whole blood. Chargaff[22,23] explained the anticoagulant effect of protamines on the basis that they combine with and inhibit the clotting activator, cephalin. Ferguson[24] expressed the opinion that salmine was antiprothrombic in the first phase and fibrinoplastic in the second phase of blood clotting. Mylon and his co-workers[15] said that prolongation of the blood clotting time undoubtedly resulted from the partial precipitation of fibrinogen. Tocantins[25] has shown that plasma to which an appropriate amount of protamine has been added will show a prolongation of the plasma clotting time and the appearance of a degree of antithromboplastic activity closely resembling that observed in hemophilic plasma. No abnormal acceleration of coagulation time of whole blood in vivo was observed during this study.

It was observed that the speed of injection of salmine sulfate is an important factor in producing toxic reactions in animals. The more slowly it was administered, the less frequent were the toxic reactions. For this reason, ten minutes were allowed for the injection of salmine into man. Although this is an arbitrary time limit, the slow intravenous injection of salmine into man is to be recommended.

Since the risk of hemorrhage from the intermittent intravenous injection of heparin is minimal, the need for protamines will not be great. In a few cases, particularly those in which operation is performed and prompt neutralization of heparin is desired, this protamine should be of value. With the subcutaneous and intramuscular administration of heparin in delaying menstruums and with new developments in the field of vascular surgery, a need for rapid and effective control of heparin becomes apparent.

SUMMARY AND CONCLUSIONS

The protamine, salmine, was found to have toxic effects when it was administered intravenously in large doses to guinea pigs, rabbits, and dogs. When small doses, such as 1.0 mg. per kilogram, were administered, toxic effects were not noted.

Salmine neutralized the anticoagulant effect of intravenous injections of heparin into dogs. When heparin in Pitkin's menstruum was injected intramuscularly into dogs, the elevated coagulation time returned to normal temporarily after the intravenous injection of salmine.

In man, the intravenous injection of 40 to 50 mg. of salmine sulfate neutralized promptly the anticoagulant effect of 50 mg. of heparin, and when salmine sulfate was administered slowly in these doses it did not produce any reactions.

ACKNOWLEDGMENT

We wish to express our appreciation to Dr. H. E. Essex and Dr. C. F. Code for their aid in carrying out the investigation which we are reporting and for the provision of facilities at the Institute of Experimental Medicine of the Mayo Foundation and in the Section of Physiology of the Mayo Clinic.

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A COMPARISON OF PRECORDIAL ELECTROCARDIOGRAMS OBTAINED WITH CR, CL, CF, AND V LEADS

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PRECORDIAL leads in which the indifferent electrode is placed on one of the extremities do not record the true electrical changes occurring at the precordium, but are subject to distortions resulting from the potential variations of the indifferent electrode. The nature and magnitude of the distortion will vary, depending, among other things, on the anatomic position of the heart in the thorax. Although this has been recognized for some time, it has been assumed by many that these distortions are small in magnitude and do not influence the interpretation of the precordial electrocardiogram. Among the several attempts to obtain a true unipolar lead, one which is free from such distortion, the central terminal method of Wilson[1] has received the widest attention in clinical electrocardiography. It can be shown mathematically that the potential of the central terminal is equal to zero, provided that (a) the heart is considered electrically equivalent to a small dipole, (b) the body is considered a large homogeneous volume conductor, (c) the extremities are considered to form the apices of an equilateral triangle in the center of which the heart is located, and (d) the heart and extremities are considered to lie in the same plane.[1,2] Considerable difference of opinion exists as to the accuracy of these assumptions. Actual measurement of the potential of the central terminal has shown it to be not greater than 0.3 to 0.36 mv.,[3,4,5,6] that is, 3.0 to 3.5 mm., in tracings as ordinarily standardized.

Several studies have been made comparing precordial leads obtained with the indifferent electrode on the right arm, left arm, left leg, and, in some studies, with the chest electrode connected to the central terminal.[7,8,9a,9b,9c,10,11,12] The results of these studies have been uniform in demonstrating that differences between CR, CL, CF, and V leads do exist, but the conclusions derived have been divergent. Groedel,[9a] Wolferth and Wood,[13] and Alzamora Castro[12] stated that the type of precordial lead used could influence the interpretation of the electrocardiogram, whereas Hayos and Tomayo[10] concluded that the observed differences were essentially unimportant. In a previous communication from this laboratory, the latter view was upheld.[8] The results of the present study necessitate some revision of the conclusions stated in the previous paper. It is

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the purpose of this report to describe the differences among CR, CL, CF, and V leads taken at identical precordial positions and to cite four types of electrocardiograms we have observed in which these differences may influence the interpretation of the electrocardiogram.

MATERIAL AND METHOD

Standard limb, precordial, and aV extremity leads (taken by the Goldberger method,[14] but with the 5,000 ohm resistances retained) were taken on a group of forty-four normal adults of varying ages. The seven precordial positions were used, and at each one, without the chest electrode being moved, the indifferent electrode was attached in turn to the right arm, left arm, left leg, and the central terminal by means of a lead selector switch. Similar electrocardiograms were taken on patients with posterior wall infarction and pulmonary emphysema and on others who showed electrocardiographic abnormalities thought to be partly due to the effect of the potential of the indifferent electrode.

The amplitudes of the various deflections in the normal group were measured and tabulated according to the direction of the QRS axis. The mean and range were determined for each precordial position and for the aV leads. The values for the QRS and T deflections in the V extremity leads (obtained by multiplication of the deflections in the aV leads by two-thirds) were subtracted algebraically from the corresponding deflection in the V precordial lead to obtain the predicted CR, CL, and CF lead at the given position. The values so obtained were compared with the observed values in the CR, CL, and CF leads and the differences noted.

RESULTS

1. The minimum, maximum, and mean deflection of P, R, S, and T as observed in the different types of precordial leads are listed in Tables 1,*A*, 1,*B*, and 1,*C*. The P and T deflections were tallest in CR leads and smallest in CF leads at all precordial positions for all directions of the QRS axis. The R wave was tallest in CR leads and smallest in CF leads when the QRS axis was plus 35° to plus 90°, and smallest in CL leads when the QRS axis was 0° to plus 34°. The S wave was largest in CL leads when the direction of the QRS axis was to the left of plus 35° and largest in CF leads when the QRS axis was to the right of plus 35°. All the deflections in V leads tended to resemble CL leads when the direction of the QRS axis was to the right of 35°. The R and S deflections tended to resemble those in CF leads when the direction of the QRS axis was to the left of plus 35°. However, the P and T deflections in V leads resembled those in CL leads rather than in CF leads as would be expected. The explanation for this is not entirely clear. No significant differences were observed in regard to Q waves or S-T deviations.

TABLE 1,A. THE AMPLITUDE OF THE DEFLECTIONS IN VARIOUS PRECORDIAL LEADS (QRS AXIS 0 TO +34°; TEN SUBJECTS)

DEFLECTION	PRECORDIAL POSITION	CR MIN. (MM.)	CR MEAN (MM.)	CR MAX. (MM.)	CF MIN. (MM.)	CF MEAN (MM.)	CF MAX. (MM.)	CL MIN. (MM.)	CL MEAN (MM.)	CL MAX. (MM.)	V MIN. (MM.)	V MEAN (MM.)	V MAX. (MM.)
P	1	0.3	0.9	1.6	−1.1	−0.4	0.8	0.8	0.4	1.5	0	0.4	1.2
	2	−1.1	0.9	2.0	−0.8	0.1	0.8	0.3	0.7	1.4	0.1	0.6	1.4
	3	0.4	1.0	1.9	−0.5	−0.2	0.3	0.1	0.5	0.9	0.1	0.4	0.8
	4	0.8	1.0	1.7	−0.3	0.1	0.6	0.2	0.5	1.1	0.2	0.4	0.9
	5	0.7	1.0	1.4	−0.2	0.1	0.2	0.1	0.4	1.1	0.2	0.4	0.6
	6	0.6	1.1	1.8	−0.2	0.1	0.2	0	0.3	0.9	0.2	0.3	0.5
	7	0.5	0.9	1.2	−0.3	0	0.3	0	0.3	1.0	0.2	0.4	0.5
R	1	0.6	3.3	7.8	0	1.8	4.2	0.6	2.3	4.1	0.2	2.3	4.7
	2	2.4	7.9	13.9	1.0	5.1	8.9	1.6	4.5	7.1	1.6	5.6	9.4
	3	4.7	14.3	23.9	2.4	7.6	17.9	4.1	7.5	13.5	3.1	9.8	18.8
	4	9.1	19.3	27.8	3.2	12.0	20.9	2.9	11.0	19.1	5.8	13.9	22.0
	5	13.8	20.4	28.0	8.8	13.8	25.2	4.8	11.7	24.8	10.4	15.7	28.4
	6	11.5	16.9	29.8	6.1	10.3	22.5	5.2	9.2	18.0	7.1	12.1	23.8
	7	10.8	15.0	20.7	4.5	7.7	13.5	3.5	6.7	9.8	6.6	9.2	14.0
S	1	0.3	5.9	10.6	3.5	10.7	15.9	4.9	12.5	18.3	3.2	9.3	13.1
	2	2.5	9.3	18.8	3.3	12.2	25.5	4.8	13.2	26.2	3.8	11.4	24.1
	3	0	6.0	15.8	0.8	7.0	16.5	2.0	8.4	17.1	1.3	7.0	16.9
	4	0	3.3	9.8	0	3.7	8.7	0	3.0	11.4	0	3.5	7.8
	5	0	0.6	1.9	0	0.5	1.5	0	0.8	2.2	0	0.6	1.7
	6	0	0.2	0.9	0	0.1	0.9	0	0.4	1.7	0	0.2	1.0
	7	0	0	0.2	0	0	0	0	0.3	1.9	0	0	0
T	1	0.3	1.5	3.2	−3.2	−1.0	1.4	−2.9	−0.9	1.2	−2.2	0.3	1.8
	2	2.9	5.2	9.9	−0.5	3.2	7.0	1.2	3.4	5.7	0.6	3.9	7.5
	3	3.9	6.3	9.9	2.5	4.2	5.9	2.8	4.3	6.2	3.2	4.8	7.0
	4	2.9	5.3	10.2	2.1	3.9	6.0	1.4	4.2	7.5	2.8	4.6	7.9
	5	1.7	5.0	8.1	0.8	2.7	4.9	0.6	3.2	5.9	1.4	3.6	6.4
	6	0.8	4.1	7.9	0.4	1.8	3.8	0.2	2.3	4.7	0.8	2.8	4.9
	7	1.1	3.6	6.5	0	1.2	2.7	1.1	1.6	3.3	0.8	2.2	3.9

TABLE 1,*B*. THE AMPLITUDE OF THE DEFLECTIONS IN VARIOUS PRECORDIAL LEADS (QRS AXIS +35° TO +59°; TWELVE SUBJECTS)

DEFLECTION	PRECORDIAL POSITION	CR			CF			CL			V		
		MIN. (MM.)	MEAN (MM.)	MAX. (MM.)	MIN. (MM.)	MEAN (MM.)	MAX. (MM.)	MIN. (MM.)	MEAN (MM.)	MAX. (MM.)	MIN. (MM.)	MEAN (MM.)	MAX. (MM.)
P	1	0.5	1.0	2.0	−1.5	0	0.3	−0.2	0.4	1.1	0	0.6	3.0
	2	0.5	0.9	1.4	−1.0	0.1	0.4	0	0.5	0.9	0.3	0.5	0.9
	3	0.2	0.9	1.4	−0.5	0.1	0.9	0.2	0.5	0.9	0.2	0.4	0.8
	4	0.3	1.0	1.4	−0.2	0.1	0.4	0.2	0.5	0.9	0.1	0.4	0.7
	5	0.5	0.9	1.4	−0.2	0.2	0.3	0	0.3	0.8	0	0.4	0.7
	6	0.3	0.9	1.2	−0.2	0.1	0.3	0	0.4	0.7	0	0.3	0.6
	7	0.3	0.8	1.1	−0.5	0	0.4	0	0.3	0.9	0.2	0.3	0.5
R	1	1.3	4.7	6.4	1.2	3.2	4.9	1.1	3.5	6.7	1.4	3.7	5.2
	2	1.5	8.9	19.9	1.2	5.6	10.0	1.8	5.9	9.0	1.5	6.7	12.9
	3	2.1	14.4	27.2	1.1	7.2	16.7	1.5	8.8	12.6	1.7	10.1	18.9
	4	12.2	20.7	29.0	7.4	11.7	19.9	9.4	14.5	21.9	7.8	15.5	22.6
	5	15.9	19.4	26.8	3.8	10.9	20.2	8.9	13.5	21.2	10.8	14.6	19.9
	6	11.5	16.0	21.6	4.2	7.1	17.1	5.6	10.1	20.1	7.6	10.9	18.7
	7	9.1	13.1	16.7	0.3	4.6	12.2	3.0	7.6	15.1	5.7	8.2	13.8
S	1	2.9	8.4	14.6	9.8	14.4	21.9	3.8	12.1	18.8	5.2	11.4	18.7
	2	2.1	10.1	16.3	3.6	13.9	21.9	4.1	12.5	20.8	5.0	11.9	18.9
	3	0	5.5	11.4	0.9	6.9	13.9	0.7	6.0	9.8	0.5	6.2	10.8
	4	0	2.4	8.2	0	2.9	10.9	0	2.7	8.1	0	2.6	8.1
	5	0	0.9	3.1	0	1.3	5.7	0	0.9	1.5	0	0.9	3.3
	6	0	0.4	1.8	0	0.3	2.5	0	0.4	2.4	0	0.3	1.1
	7	0	0.3	1.6	0	0.1	1.4	0	0.1	0.8	0	0.1	0.6
T	1	1.1	3.1	6.6	−4.6	0	3.5	−1.1	1.2	4.2	−3.2	1.0	3.8
	2	3.0	5.5	11.9	−0.8	3.9	8.6	1.1	4.4	11.0	1.2	4.7	11.5
	3	2.9	6.2	12.0	1.5	3.9	8.9	2.0	4.3	9.7	2.2	3.9	10.2
	4	2.1	5.7	10.2	1.8	3.3	4.7	1.5	3.9	6.5	1.8	4.4	7.7
	5	2.0	5.0	11.1	0.9	2.3	4.8	0.8	3.1	7.3	1.2	3.5	7.5
	6	1.8	4.1	8.9	0.1	1.5	3.5	0.4	2.1	4.7	0.8	2.5	5.9
	7	0.8	3.4	7.1	−0.2	0.9	2.7	0	1.7	3.5	0.3	2.0	4.1

TABLE 1,C. THE AMPLITUDE OF THE DEFLECTIONS IN VARIOUS PRECORDIAL LEADS (QRS AXIS +60° TO +90°; TWENTY-TWO SUBJECTS)

DEFLECTION	PRECORDIAL POSITION	CR			CF			CL			V		
		MIN. (MM.)	MEAN (MM.)	MAX. (MM.)	MIN. (MM.)	MEAN (MM.)	MAX. (MM.)	MIN. (MM.)	MEAN (MM.)	MAX. (MM.)	MIN. (MM.)	MEAN (MM.)	MAX. (MM.)
P	1	−0.3	0.9	1.5	−1.5	−0.9	0.7	0	0.6	1.1	−0.4	0.5	1.0
	2	0.3	0.9	1.4	−1.5	−0.4	1.0	0.3	0.6	0.9	−0.3	0.7	0.9
	3	0.6	1.0	1.9	−1.0	0.2	0.5	0.2	0.6	1.5	0.2	0.5	1.1
	4	0.5	1.0	1.7	−0.5	−0.1	0.5	0.2	0.6	1.1	0.3	0.5	1.1
	5	0.6	1.1	1.8	−0.5	−0.1	0.3	0	0.6	1.4	0.1	0.5	1.1
	6	0.9	1.2	1.9	−0.6	−0.1	0.2	0.1	0.6	1.1	0.2	0.5	1.1
	7	0.7	1.1	1.7	−0.5	−0.1	0.2	0	0.6	1.2	0.2	0.6	1.3
R	1	0.8	4.0	9.7	0.8	2.2	7.7	1.1	3.1	6.9	1.5	3.3	6.9
	2	1.4	6.6	14.2	2.1	5.4	12.9	2.1	5.3	11.8	2.1	5.3	12.7
	3	5.4	10.9	28.0	2.2	6.6	17.3	3.0	8.5	24.7	4.1	8.7	23.5
	4	7.8	18.2	30.9	1.4	8.4	18.4	3.8	15.0	30.6	6.1	14.3	27.1
	5	4.9	17.7	29.5	0.8	6.2	13.3	7.8	14.3	27.1	5.8	12.9	21.8
	6	4.9	15.6	24.9	0.5	3.5	7.6	4.2	11.9	23.0	6.1	10.4	16.2
	7	3.1	13.1	19.5	0	1.9	5.2	3.9	10.2	18.6	4.2	8.6	15.7
S	1	3.3	9.7	18.4	3.8	18.9	28.8	1.7	10.9	25.8	2.2	12.7	25.9
	2	2.9	13.6	22.4	12.1	21.3	30.1	7.9	14.8	24.3	6.8	16.2	23.6
	3	0	9.3	19.8	0	13.4	29.2	0	8.7	19.1	0	10.2	21.1
	4	0	4.9	13.9	0	7.0	23.9	0	3.7	12.9	0	5.0	13.9
	5	0	1.4	4.4	0	2.1	7.9	0	0.7	3.9	0	1.1	5.1
	6	0	0.8	4.1	0	1.0	4.2	0	0.4	2.9	0	0.6	2.6
	7	0	0.6	2.7	0	0.8	3.1	0	0.2	1.8	0	0.3	1.4
T	1	−0.2	2.8	6.7	−2.4	−0.2	3.2	−1.9	1.7	5.7	−1.4	1.3	6.0
	2	0.2	6.5	11.9	−1.2	4.5	8.2	−0.6	5.4	10.1	−0.3	5.6	9.8
	3	0.8	7.3	12.9	−0.3	4.7	8.5	−0.3	5.7	10.8	−0.2	5.5	10.6
	4	2.2	6.6	10.9	0.2	3.6	7.9	0.2	4.7	9.0	1.4	5.0	9.1
	5	2.2	5.2	8.2	0	2.3	5.0	1.1	3.2	5.4	0.9	4.0	5.3
	6	1.8	4.1	5.8	−0.7	1.1	2.7	0.9	2.3	3.9	0.8	2.6	3.8
	7	1.4	3.4	5.5	−0.7	0.5	1.2	0.3	1.9	3.6	0.8	2.2	3.9

Table 2,A. The Predicted and Observed Values for the Mean QRS Deflections

	QRS axis 0° to +34°							QRS axis +35° to +59°							QRS axis +60° to +90°						
	Precordial position							Precordial position							Precordial position						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
V Observed	-7.0	-5.8	2.7	12.1	14.7	11.3	8.8	-13.5	-5.2	3.7	12.6	13.3	10.1	7.6	-9.4	-10.9	-1.6	9.2	11.5	9.3	7.8
V_R Observed				-7.5							-5.7							-5.1			
V_L Observed				2.5							0.7							-1.9			
V_F Observed				1.0							3.3							6.4			
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
CR Predicted	0.5	1.7	10.2	19.6	22.2	18.8	16.3	-7.8	0.5	9.4	18.3	19.0	15.8	13.3	-4.3	-5.8	3.5	14.3	16.6	14.4	12.9
CR Observed	-2.6	-1.4	8.2	15.3	17.9	16.0	14.4	-3.7	-1.2	8.8	17.6	17.9	14.9	12.1	-5.7	-7.0	1.5	13.1	15.7	14.1	11.8
CR Difference	3.1	3.1	2.0	4.3	4.3	2.8	1.9	4.1	1.7	0.6	0.7	1.1	0.9	1.2	1.4	1.2	2.0	1.2	0.9	0.3	1.1
CL Predicted	-9.5	-8.3	0.2	9.6	12.2	8.8	6.3	-14.2	-5.9	3.0	11.9	12.6	9.4	6.9	-7.5	-9.0	0.3	11.1	13.4	11.2	9.7
CL Observed	-10.2	-8.7	-1.0	7.8	10.6	7.1	6.1	-8.6	-6.6	2.7	11.6	12.3	9.3	7.1	-7.8	-9.5	-0.3	11.2	13.1	10.8	9.4
CL Difference	0.7	0.4	1.2	1.8	1.6	1.7	0.2	5.6	0.7	0.3	0.3	0.3	0.1	0.2	0.3	0.5	0.6	0.1	0.3	0.4	0.3
CF Predicted	-8.0	-6.8	1.7	11.1	13.7	10.3	7.8	-16.8	-8.5	0.4	9.3	10.0	6.8	4.3	-15.8	-17.3	-8.0	2.8	5.1	2.9	1.4
CF Observed	-8.9	-7.1	0.5	8.0	11.7	9.4	7.1	-11.2	-8.3	0.2	8.5	9.0	6.1	3.8	-16.7	-15.9	-6.9	1.3	3.9	2.2	0.5
CF Difference	0.9	0.3	1.2	3.1	2.0	0.9	0.7	5.6	0.2	0.2	0.8	1.0	0.7	0.5	0.9	1.4	1.1	1.5	1.2	0.7	0.9

TABLE 2,*B*. THE PREDICTED AND OBSERVED VALUES FOR THE MEAN T DEFLECTIONS

	QRS AXIS 0° TO +34°							QRS AXIS +35° TO +59°							QRS AXIS +60° TO +90°						
	PRECORDIAL POSITION							PRECORDIAL POSITION							PRECORDIAL POSITION						
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
V Observed	0.3	3.9	4.8	4.6	3.6	2.8	2.2	1.0	4.7	3.9	4.4	3.5	2.5	2.0	1.3	5.6	5.5	5.0	4.0	2.6	2.2
V_R Observed				–1.7							–1.5							–1.5			
V_L Observed				0.6							0.5							0.3			
V_F Observed				0.8							1.2							1.4			
	1	2	3	4	5	6	7	1	2	3	4	5	6	7	1	2	3	4	5	6	7
CR Predicted	2.0	5.6	6.5	6.3	5.3	4.5	3.9	2.5	6.2	5.4	5.9	5.0	4.0	3.5	2.8	7.1	7.0	6.5	5.5	4.1	3.7
Observed	1.5	5.2	6.3	5.3	5.0	4.1	3.6	3.1	5.5	6.2	5.7	5.0	4.1	3.4	2.8	6.5	7.3	6.6	5.2	4.1	3.4
Difference	0.5	0.4	0.2	1.0	0.3	0.4	0.3	0.6	0.7	0.8	0.2	0.0	0.1	0.1	0.0	0.6	0.3	0.1	0.3	0.0	0.3
CL Predicted	–0.3	3.3	4.2	4.0	3.0	2.2	1.6	0.5	4.2	3.4	3.9	3.0	2.0	1.5	1.0	5.3	5.2	4.7	3.7	2.3	1.9
Observed	–0.9	3.4	4.3	4.2	3.2	2.3	1.6	1.2	4.4	4.3	3.9	3.1	2.1	1.7	1.7	5.4	5.7	4.7	3.2	2.3	1.9
Difference	0.6	0.1	0.1	0.2	0.2	0.1	0.0	0.7	0.2	0.9	0.0	0.1	0.1	0.2	0.7	0.1	0.5	0.0	0.5	0.0	0.0
CF Predicted	–0.5	3.1	4.0	3.8	2.8	2.0	1.4	–0.2	3.5	2.7	3.2	2.3	1.3	0.8	–0.1	4.2	4.1	3.6	2.6	1.2	0.8
Observed	–1.0	3.2	4.2	3.9	2.7	1.8	1.2	0.0	3.9	3.9	3.3	2.3	1.5	0.9	–0.2	4.5	4.7	3.6	2.3	1.1	0.5
Difference	0.5	0.1	0.2	0.1	0.1	0.2	0.2	0.2	0.4	1.2	0.1	0.0	0.2	0.1	0.1	0.3	0.6	0.0	0.3	0.1	0.3

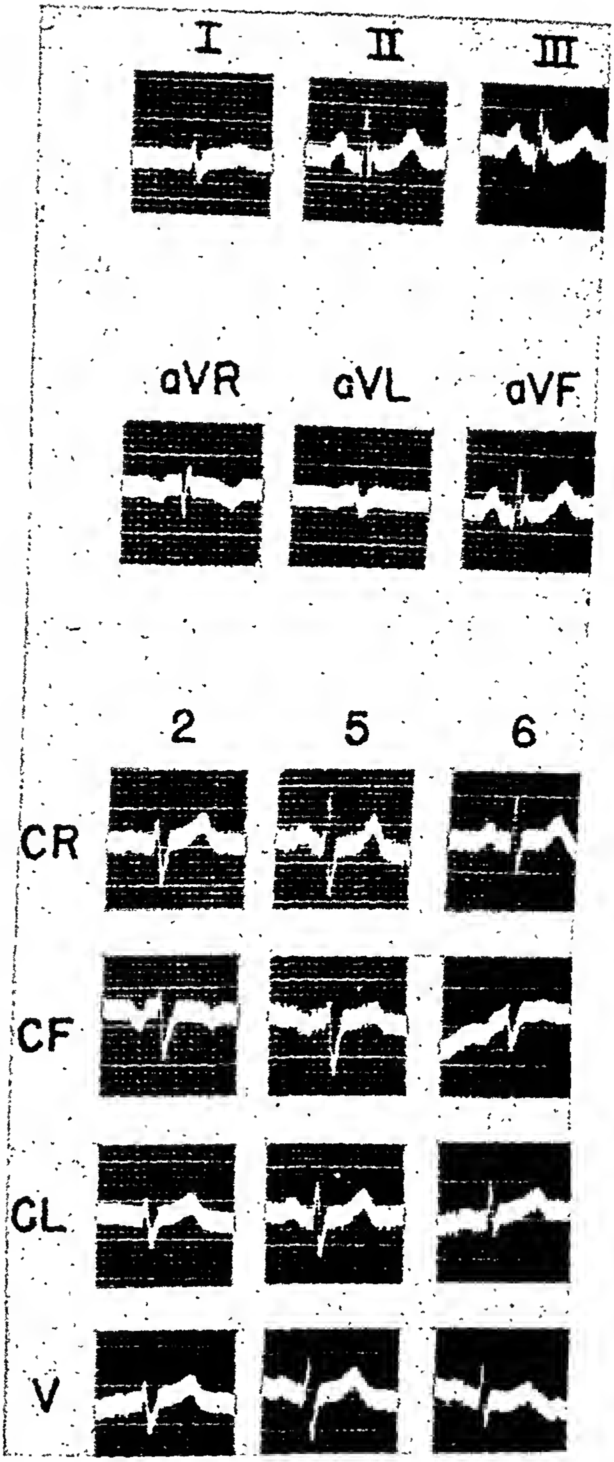

Fig. 1.—A case of pulmonary emphysema showing abnormally small R waves and relatively deep S waves in CF leads indicative of possible right ventricular preponderance; CR, CL, and V leads show normal R/S ratios. Note also T-wave inversion in Lead CF_2 as compared with upright T waves in CR_2, CL_2, and V_2. Note also the inverted P waves in the CF leads, not present in the CR, CL, or V leads. This record is definitely abnormal and shows a P-pulmonale. In a case of this sort it may be properly asked whether the abnormalities in the CF leads are more informative than the absence of such abnormalities in the CR, CL, and V leads.

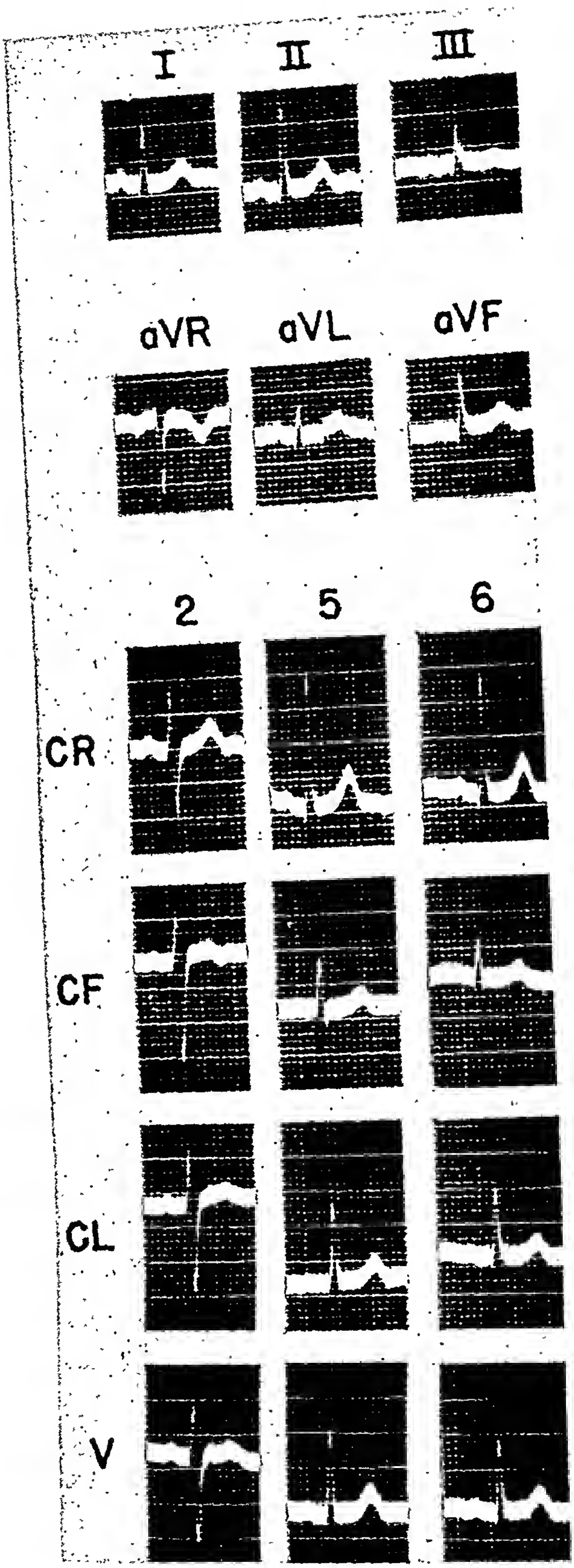

Fig. 2.—An example of an isolated inverted T wave in CF_2 and upright T waves in Leads CR_2, CL_2, and V_2 in a subject with no evidence of heart disease and no other electrocardiographic abnormalities.

2. In CF leads, as the QRS axis shifted *from* left to *right*, the P, R, and T waves, in general, decreased in amplitude, and the S waves increased in amplitude (Tables 1,*A*, 1,*B*, and 1,*C*). Changes also occurred in the other leads but were less marked than in CF. Thus, the most conspicuous differences in subjects with right axis shift occurred between CF and the other leads in positions from the left precordium. In left axis shift, the principle differences, but less conspicuous, occurred between CL and the other leads.

3. The predicted and observed values for the mean QRS and T deflections in CR, CL, and CF leads are given in Tables 2,*A* and 2,*B*. The observed values for QRS and T in the V precordial and V extremity leads are also shown. The mean error between the predicted and observed QRS was 1.3 mm. with a range of 0.1 to 5.6 millimeters. The mean error between the predicted and observed T waves was 0.3 mm. with a range of 0.0 to 1.2 millimeters.

4. We have observed four types of electrocardiograms in which the differences between CF and V leads may be sufficient to influence the interpretation of the electrocardiogram:

A. In some subjects with normal right axis shift, or with pulmonary emphysema, CF leads may record QRS complexes which have relatively small R waves and large S waves in precordial Positions 5 and 6. This precordial pattern associated with right axis shift in the limb leads may be suggestive of right ventricular preponderance. V leads (or CR or CL leads) record complexes which have a normal R/S ratio in the positions from the left precordium. An example is shown in Fig. 1.

B. Some normal adults have an inverted T wave in Lead CF_2 as an isolated finding. This may indicate an abnormal electrocardiogram. In some of these cases Lead V_2, CR_2, or CL_2 will record upright T waves. An example is shown in Fig. 2.

C. An occasional subject with normal right axis shift or pulmonary emphysema may show T-wave inversion in CF_6. This would be considered distinctly abnormal, yet V, CR, or CL leads may record upright T waves at the same position. An example is shown in Fig. 3.

The abnormalities listed in A, B, and C sometimes may all occur in the same record.

D. In some patients with healing or healed posterior wall infarction who show inverted T waves in Leads II, III, and V_F and upright T waves in CF leads, V, CR, and CL leads from precordial Positions 5 or 6 may record inverted T waves. Localization of the infarct to the posterolateral wall would be justified from the T-wave inversion in these positions. This localization could be made with V, CR, or CL leads, but not with the CF lead. An example is shown in Fig. 4.

DISCUSSION

The results of our present study confirm the work of Hecht[7] and others, indicating that precordial leads obtained by a chest-extremity method differ, depending on the extremity used, and such leads, in turn, differ from precordial leads using the central terminal as the location for the indifferent electrode.

In general, these differences follow a pattern which can be related to the direction of the QRS axis and the type of complexes recorded from the extremities. Thus, as the QRS axis shifts from left to right, the QRS and T complexes recorded at the left arm change from a mainly upward (plus) to a mainly downward (minus) deflection, and the QRS and T complexes recorded at the left leg change from a mainly downward (minus) to a mainly upward (plus) deflection. The

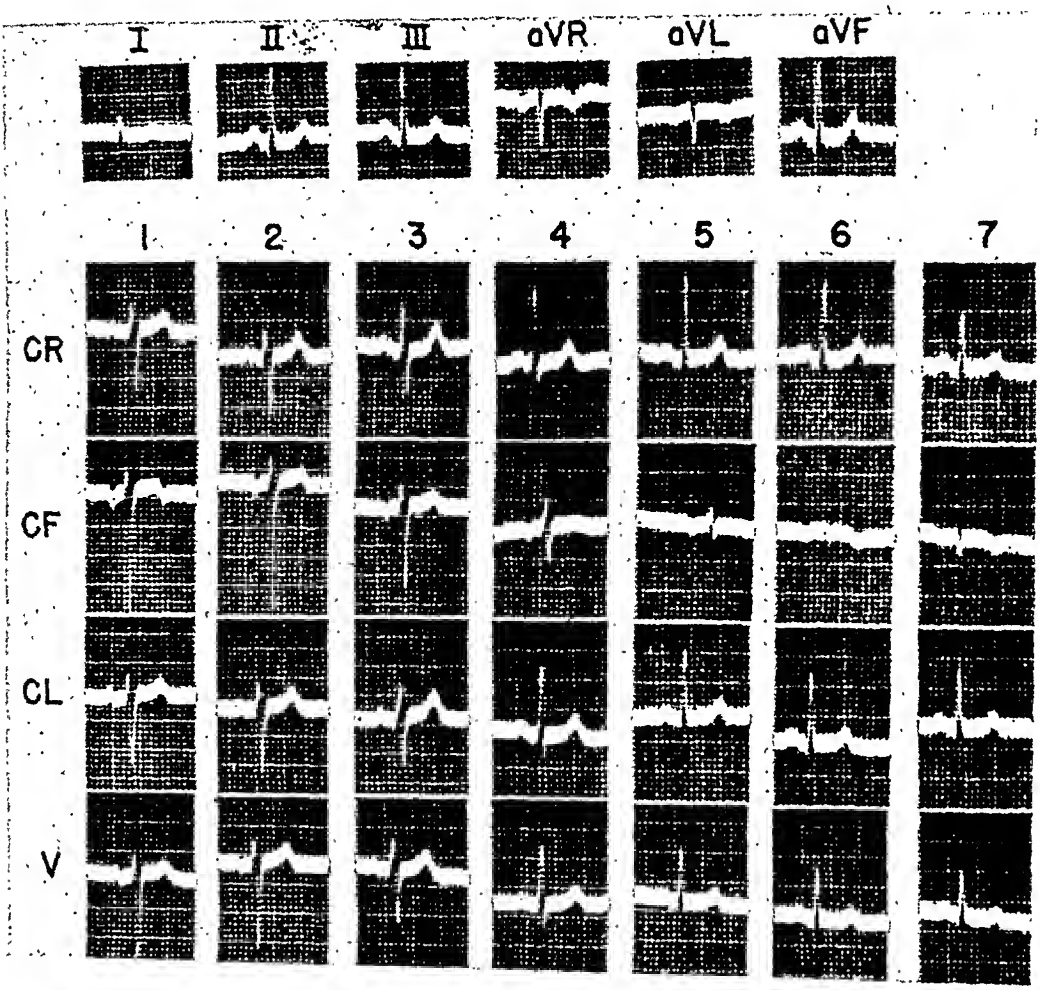

Fig. 3.—A normal subject with right axis shift showing the marked effect produced by the left leg potential in CF leads from the left precordium. There is much less difference between CL, CR, and V leads. Note also the T-wave inversion in Lead CF_6 as compared with upright T waves in CR_6, CL_6, and V_6.

QRS and T complexes recorded at the right arm are normally downward (minus), and vary relatively little with changes in the direction of the QRS axis. It would thus be anticipated that precordial leads obtained with the indifferent electrode, respectively, on the left leg or left arm would vary most with right or left axis shift (Figs. 3 and 5). The results agree for the most part with the prediction. CR and V leads do show variations as the QRS axis shifts, but they are not as conspicuous as in CF or CL leads.

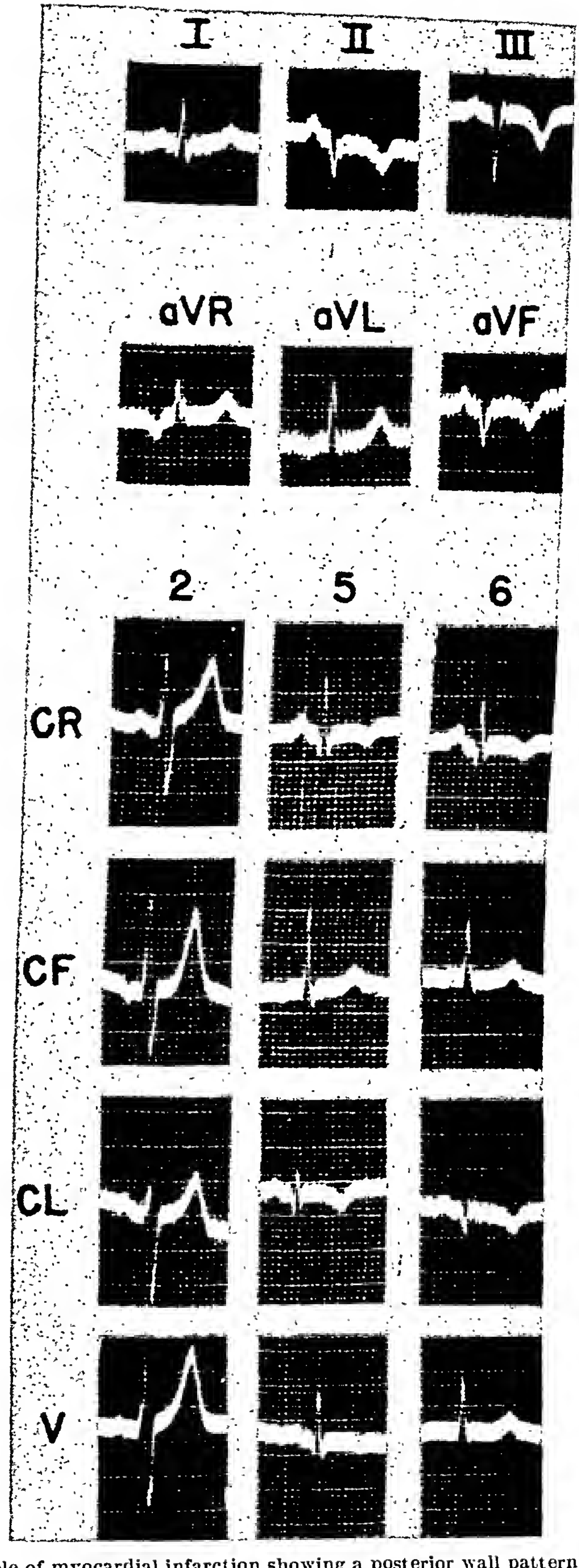

Fig. 4.—An example of myocardial infarction showing a posterior wall pattern in the limb and CF leads and a posterolateral wall pattern in CR, CL, and V leads. Leads CF_5 and CF_6 fail to show the abnormal inverted T waves seen in the CR and CL leads and, to a lesser extent, in V_5.

We have applied to our data, as an assumption, the concept that the central terminal has zero potential, in an attempt to predict accurately the amplitude of the deflections which should be obtained in CR, CL, or CF leads. Since a precordial lead records the difference in potential between the chest electrode and the extremity electrode, and if the central terminal is assumed to be constantly at zero potential, then at a given precordial position at a given instant the algebraic difference between the V precordial lead and the V extremity lead will

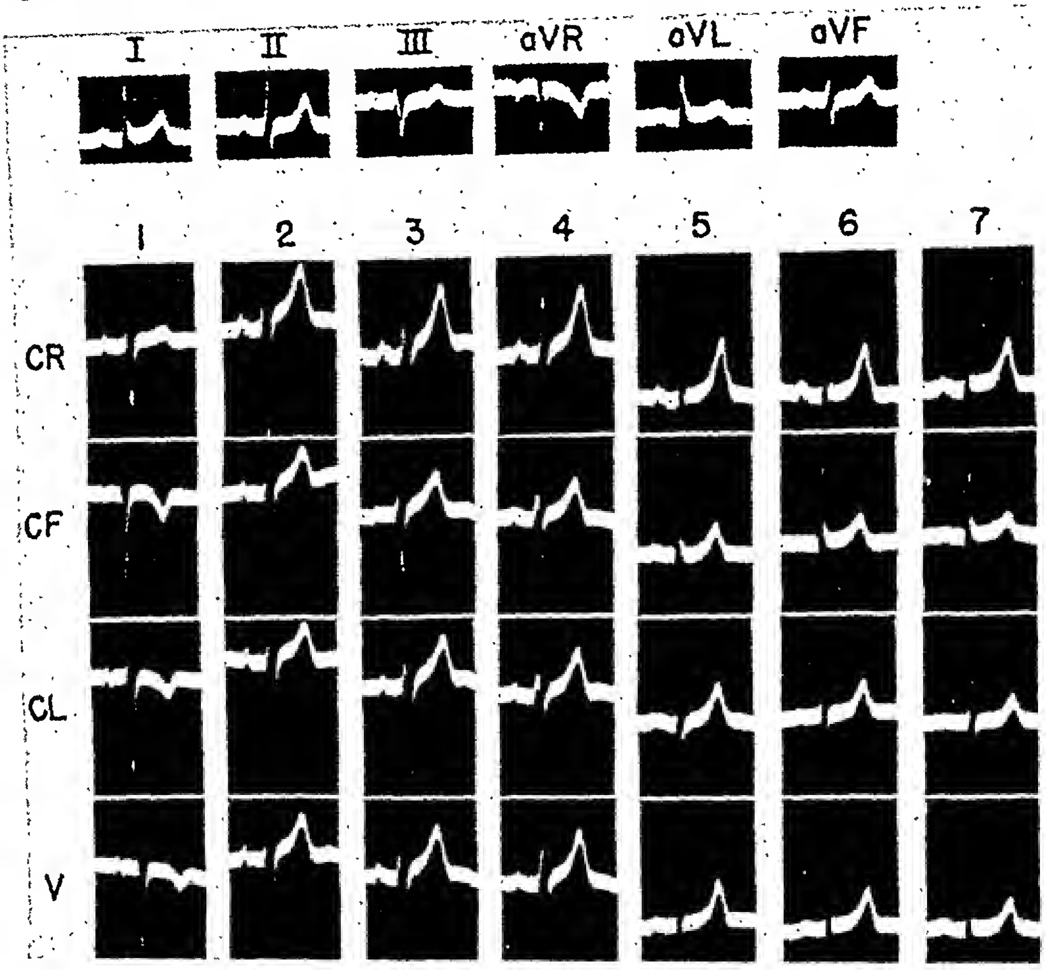

Fig. 5.—A normal subject with left axis shift showing the effect of the left arm potential on CL leads from the left precordium.

equal the precordial lead which has its indifferent electrode located on the particular extremity. The predicted and observed values are listed in Tables 2,*A* and 2,*B*. It is apparent that precise agreement between the predicted and observed values occurs relatively infrequently. Nevertheless, the mean error is small. Part of the error is undoubtedly due to measurement and part must be due to the fact that we did not obtain the precordial and V extremity leads simultaneously. But the fact remains that, with routine methods being employed, the concept that the central terminal is at zero potential does not receive rigid support from the facts. However, we do feel justified in concluding from our

data that it is possible, within a range of error, to use central terminal leads to explain and obviate the different effects exerted by the extremities on precordial leads.

For the purposes of clinical electrocardiography it is probably true that it makes little difference in the vast majority of cases whether the indifferent electrode be placed on the right arm, left arm, left leg, or attached to the central terminal. This is as would be expected since the relatively great distance of the extremity electrode from the heart, as compared with the precordial electrode, tends to minimize the influence of the indifferent electrode. In some cases, examples of which are shown, the differences are sufficient to affect the interpretation. The frequency of such cases in clinical electrocardiography is probably of the order of magnitude of 5 per cent. For the most part, these electrocardiograms show right axis shift and tall QRS complexes in the left leg resulting in small or even inverted QRS deflections in CF leads taken over the left precordium. The variations in the direction of the T wave in precordial Position 2 and the direction of T in Positions 5 or 6 in posterior wall infarction in various types of precordial leads have been pointed out previously.[12,15] It has been shown[12] that CF leads from the left precordium may fail to record prominent Q waves in posterolateral infarction, whereas V leads will record these deflections. In Fig. 4 prominent Q waves are seen only in Leads CL_5 and CL_6. The rare T-wave inversion in CF_5 or CF_6 in normal subjects which appears to be the result of the relatively tall T wave in Lead V_F and which becomes upright in V, CR, or CL leads was postulated by Hecht[7] and illustrated by Alzamora Castro.[12]

It is not possible at present to make a categorical statement as to the ideal location for the indifferent electrode. On theoretical grounds CR, CL, and CF leads are equally undesirable since all are subject to the distorting effects of the potential of the indifferent electrode. The magnitude and variability of the distortion will be most pronounced in CF and CL leads, which directly reflect change in the anatomic position of the heart. It is apparent that when the potential recorded at an extremity is large, its effect on a precordial lead is considerable, and when the extremity potential is small, its effect on a precordial lead is minimal. If the central terminal can be shown to be relatively constant in potential and consistently more indifferent than the extremities, it will be the location of choice, among those available, for the indifferent electrode.

SUMMARY AND CONCLUSIONS

1. A comparison has been made of CR, CL, CF, and V leads recorded at identical precordial positions in forty-four normal subjects and in a group of patients with posterior wall infarction, emphysema, and nonspecific electrocardiographic abnormalities in order to re-evaluate the differences among these leads and to cite instances where the differences may influence the interpretation of the electrocardiogram.

2. In general, the amplitude of the deflections was greatest in CR and smallest in CF leads. The size of the deflections varied with the direction of the QRS axis. This was most marked in CF leads which showed a progressive de-

crease in the R/S ratio as well as an absolute decrease in the size of the R and S waves in leads from the left precordium as the QRS axis shifted from left to right. Similar but less pronounced changes occurred in CL leads as the QRS axis shifted from right to left. CR and V leads remained more constant, but not absolutely so, with changes in the direction of the QRS axis.

3. The differences among CR, CL, CF, and V leads can be explained, with a relatively small mean error, on the basis of the influence of the extremity when the central terminal is used to record the precordial and extremity potentials. Within this range of error it may be said that the substitution of V precordial leads for chest-extremity lead combinations will eliminate the effect of the extremity potential on the precordial electrocardiogram.

4. Four types of electrocardiograms are illustrated: (a) those in subjects with right axis shift or with pulmonary emphysema showing a small R in Leads CF_5 and CF_6 and a normal R/S ratio in V_5 and V_6; (b) those in normal adults with isolated T-wave inversion in Lead CF_2 but not in V_2; (c) those with right axis shift or emphysema with isolated T-wave inversion in CF_6 but not in Lead V_6; and (d) those with healing or healed posterior wall infarction with an inverted T wave in Leads II, III, and V_F associated with an upright T wave in CF leads and an inverted T wave in the V leads. In these the differences between CR, CL, CF, and V leads may be of sufficient magnitude to affect the interpretation of the electrocardiogram. In these examples, the CF lead differs most from the other lead combinations. Such instances occur in about 5 per cent of cases. In the vast majority of cases it probably makes little difference whether the electrode is on the right arm, left arm, left leg, or attached to the central terminal as far as clinical interpertation is concerned.

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NEOSYNEPHRINE IN TREATMENT OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

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MECHANICAL methods of treatment are frequently unsuccessful in stopping attacks of paroxysmal supraventricular tachycardia. In some protracted attacks the effects of the rapid heart action on the circulation are sufficiently serious to justify the use of drugs in an attempt to restore normal rhythm. Quinidine is frequently effective in terminating an attack, but it does so only after a considerable and variable latent period, which makes the therapeutic evaluation of this drug difficult. Mecholyl is likewise often effective in stopping paroxysmal tachycardia, but it produces distressing side effects, which may be more disturbing than the rapid heart action itself.

In a preliminary paper we have reported the efficacy of Neosynephrine in reverting paroxysmal supraventricular tachycardia to normal rhythm.[1] Keys and Violante[2] had studied effects of Neosynephrine in various cardiac arrhythmias, and their report included two cases of paroxysmal auricular tachycardia, which were reverted to normal rhythm.

MECHANISM OF ACTION OF NEOSYNEPHRINE

Neosynephrine differs from epinephrine in that the molecule has a hydrogen atom instead of the hydroxy group in the para position on the benzene ring. In spite of their similarity chemically, the cardiovascular effects of the two drugs are quite different. The potency of Neosynephrine as a direct stimulant to the cardiac conducting mechanism is much less than that of epinephrine,[3] while its potency as a vasoconstrictor is relatively high. Therefore, when Neosynephrine is given to intact animals or man in nontoxic doses, it causes a rise in blood pressure which elicits cardioinhibitory reflexes from the aortic arch and carotid sinuses. These reflex inhibitory influences are more than sufficient to counteract the mild direct stimulating action of Neosynephrine on the sinoauricular node. When relatively large doses of Neosynephrine are given to dogs, the pacemaker may be displaced downward so that a ventricular bradycardia, on an escape basis, results. As the dosage is increased to very high levels, ventricular tachycardia is produced. Intravenous doses of 50 mg. given rapidly to each of several dogs weighing 10 to 12 kilograms produced a multifocal ventricular tachycardia.

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Neosynephrine has an accelerator action on the denervated heart.[3] In this respect it is one twenty-fifth to one fiftieth as potent as epinephrine.

It is considered that Neosynephrine, intravenously, stops paroxysmal supraventricular tachycardia by producing a sudden vasoconstriction which in turn causes a rapid rise in pressure in the aortic arch and carotid sinuses. Consequently, all four afferent pathways concerned with reflex cardiac slowing are simultaneously activated. These buffer reflexes are very sensitive in unanesthetized animals and in man, and only a moderate rise in blood pressure is required to cause considerable cardiac inhibition.

Theoretically, compounds which produce a slower and more prolonged rise in blood pressure than that caused by Neosynephrine would probably be

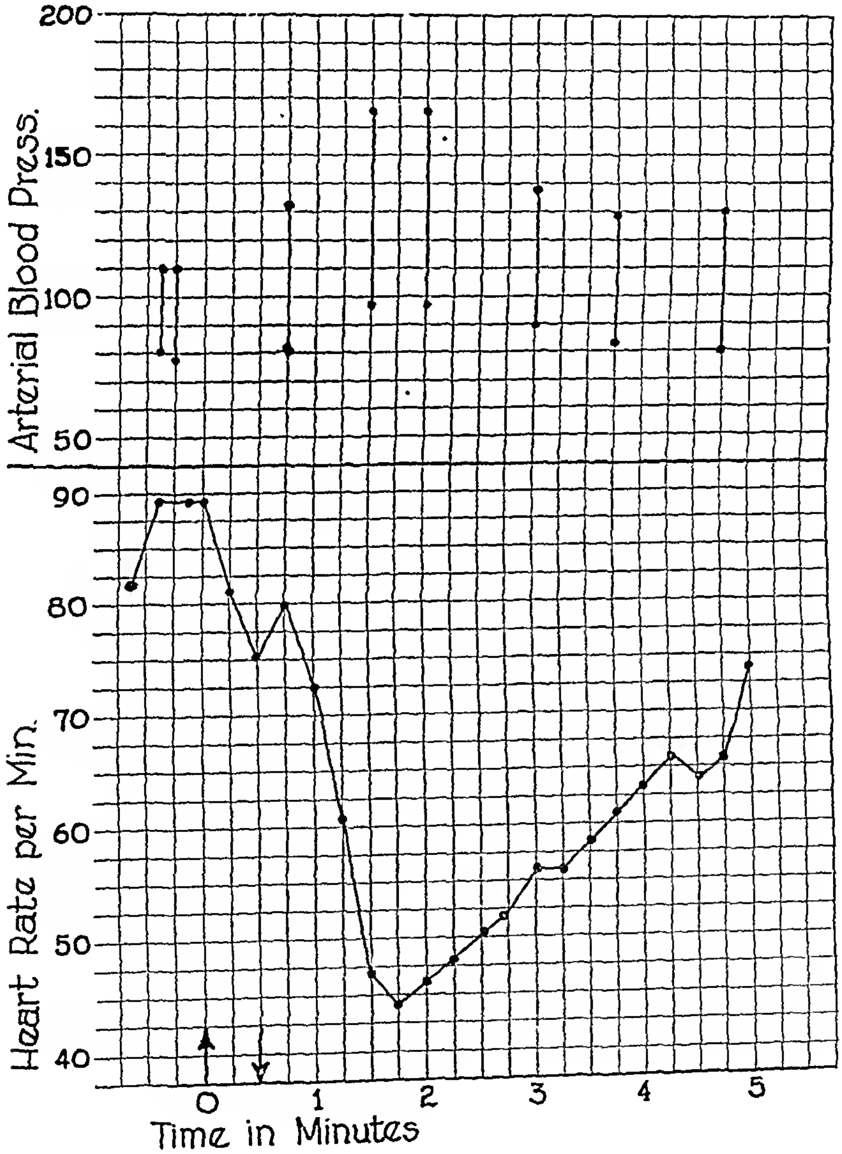

Fig. 1.—Typical changes in heart rate and blood pressure produced by intravenous injection of 0.30 mg. of Neosynephrine during the period of thirty seconds indicated by the arrows. Normal young man.

less effective as cardioinhibitors. Furthermore, administration of Neosynephrine by any route other than the intravenous one is less desirable, for it produces a more gradual, less predictable, and more prolonged rise in arterial pressure.

NEOSYNEPHRINE IN NORMAL HUMAN SUBJECTS

The cardiovascular actions of Neosynephrine in man have been studied by Keys and Violante[2] and by Hecht and Anderson.[4] We have studied effects of rapid intravenous injection of 0.30 mg. of Neosynephrine in seven normal human subjects for the purpose of determining the extent and duration of the changes

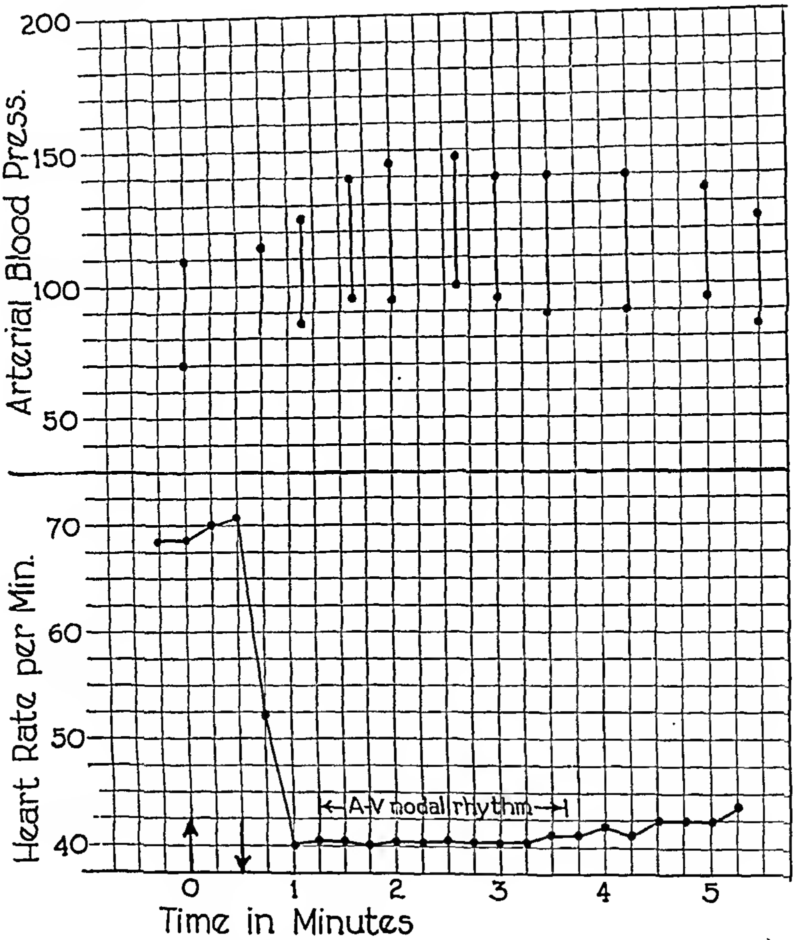

Fig. 2.—Production of a slow A-V nodal rhythm in a normal young man by injection of 0.30 mg. of Neosynephrine during the period of thirty seconds indicated by the arrows.

in blood pressure and heart rate. Continuous electrocardiograms were recorded during each experiment. The Neosynephrine was injected intravenously within twenty to thirty seconds. Forty-five seconds after the beginning of the injection in each case, the systolic and diastolic pressures were noted to be rising and the heart rate decreasing. The extent of the rise in systolic pressure varied considerably in different individuals. The minimal rise produced was 10 mm. Hg

TABLE I. EFFECT OF NEOSYNEPHRINE ON PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA

CASE	AGE	SEX	BLOOD PRESSURE BETWEEN ATTACKS	ATTACK NUMBER	DATE	HEART RATE	SYSTOLIC BLOOD PRESSURE DURING ATTACK	I. V. NEOSYNEPHRINE		
								DOSE (MG.)	MAXIMUM SYSTOLIC PRESSURE PRODUCED (MM. HG)	TIME FROM BEGINNING OF INJECTION TO REVERSAL*
1 J. B.	38	F	155/85	1	12/25/46	185	105	2.5	210	50 sec.
				2	2/17/47	185	125	0.8	202	45 sec.
				3	2/22/47	185	100	0.5 0.8 1.0	130 140 155	U U 70 sec.
				4	10/25/47	208	110	0.8 1.0	144 200	U 60 sec.
				5	11/ 2/47	220	104	0.5	134	75 sec.
				6	11/18/47	190	110	5.0	210	40 sec.
2 K. H.	51	F	140/90	1	1/22/47	165	110	0.3 0.6 0.8	140 150 160	U U 45 sec.
				2	3/15/47	176	146	0.8 1.0	210 218	U 70 sec.
3 G. M.	20	F		1	1/31/47	170	110	0.4	140	45 sec.
4 I. H.	44	M	130/84	1	2/13/47	210	80	0.8	120	45 sec.
5 P. F.†	45	F	120/70	1	2/15/47	180	104	0.5 1.0 1.5 1.9	120 135 145 156	U U U U

6	S. G.†	53	F	190/100	1	2/19/47	150-164	90	0.3 0.5 0.5 0.8	115 120 150 170	U U U U
7	M. S.	65	F	180/110	1	3/28/47	166	110	1.0	Not taken	60 sec.
9	A. B.	59	F	110/68	1	5/26/47	160	76	10.0	Not taken	less than 60 sec.
10	A. W.	28	M	120/76	1	7/12/47	170	96	0.5	142	35 sec.
					2	7/30/47	168	84	0.5	136	45 sec.
					3	8/13/47	220	98	0.5	133	62 sec.
					4	10/16/47			0.5		less than 60 sec.
					5	10/23/47			0.5		less than 60 sec.

Case 8—Ventricular tachycardia, therefore not included in this table.
*U = unsuccessful.
†Postoperative

and the maximal was 50 mm. of mercury. The diastolic pressure rose less than the systolic. The maximal pressure was attained during the period ninety to one hundred fifty seconds after the beginning of the injection. The heart rate began to decrease precipitously during the period from thirty to ninety seconds after the drug was given and reached the lowest level, usually in the range from 40 to 56 beats per minute, ninety to one hundred fifty seconds from the beginning of the injection. Blood pressure and heart rate gradually returned to the pre-injection level within seven to ten minutes after the drug was administered.

Data from two of these records are shown graphically in Figs. 1 and 2. In Fig. 1 a typical response is illustrated. Occasionally the pacemaker is displaced so that an auriculoventricular nodal rhythm is produced as indicated in Fig. 2.

TERMINATION OF ATTACKS OF PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA WITH NEOSYNEPHRINE

We have data on the use of Neosynephrine in the treatment of nineteen attacks of paroxysmal supraventricular tachycardia. The drug produced reversion to the normal rhythm in seventeen attacks in seven patients. It failed in two cases in which the attacks developed following major surgical procedures. The results are summarized in Table I, and brief case histories are presented below.

Case 1.—J. B., a 38-year-old white woman, had experienced frequent attacks of paroxysmal auricular tachycardia for ten years. The episodes lasted from fifteen minutes to several hours and had become increasingly more difficult to stop. Her blood pressure between attacks ranged from 155/85 to 120/80. Previously she had controlled her attacks with hypnotics, and, following a sound sleep, she would usually awaken with a normal rhythm. Carotid sinus massage was never effective. Since 1944 attacks had been controlled successfully with Mecholyl. More recently larger doses of this drug were found necessary to stop the attacks, and gastrointestinal side effects were very disturbing.

On Dec. 25, 1946, at 11:00 A.M. she developed persistent tachycardia which did not respond to 100 mg. of Mecholyl, 15 mg. of morphine sulfate, 180 mg. of intravenous sodium amytal, and 90 mg. of Nembutal by mouth, all given over a period of four hours. Carotid sinus massage and ocular pressure were also ineffective. At 6:30 P.M. her heart rate was 185 per minute and her blood pressure 105/80. Neosynephrine, 2.5 mg., was given intravenously. The systolic pressure rose to 160 mm. Hg within fifty seconds, at which time the tachycardia terminated abruptly. The systolic pressure continued to rise to 210, and the patient experienced mild transitory precordial discomfort. The blood pressure returned to the preinjection level in four minutes.

On Feb. 17, 1947, she was again seen with a heart rate of 185 and systolic pressure of 128 mm. of mercury. The attack had been in progress for two hours. Neosynephrine, 0.8 mg., intravenously, produced a rise of the systolic arterial pressure to 198 mm. Hg, and a normal sinus rhythm appeared forty-five seconds after the injection of the drug was begun (Fig. 3).

On Feb. 22, 1947, the patient was seen one hour after the onset of another attack of tachycardia. Her systolic pressure on this occasion was 100 mm. of mercury. A dose of 0.5 mg. of Neosynephrine caused a rise in systolic pressure to 130, but did not revert the tachycardia. Because of precordial pain radiating to the left arm, which she frequently had with attacks, she was given nitroglycerin, 0.4 mg., under the tongue. Ten minutes later Neosynephrine, 0.8 mg., raised the systolic pressure only to 130. It was concluded that the absence of an effective pressure rise was due to the nitroglycerin. Thirty minutes later 1.0 mg. of Neosynephrine given intravenously raised the systolic pressure to 155 mm. Hg, and in seventy seconds the rhythm reverted to normal (Fig. 4).

On Oct. 25, 1947, the patient was seen again with tachycardia. Neosynephrine, 0.8 mg., produced a rise of systolic pressure to 144 but did not stop the attack. Ten minutes later the tachycardia yielded to 2.0 mg. of Neosynephrine, which raised the systolic pressure to 200 mm. of mercury. On Nov. 2, 1947, a fifth attack was reverted with 0.5 mg. of Neosynephrine, which produced a systolic pressure of 134 mm. Hg in seventy-five seconds.

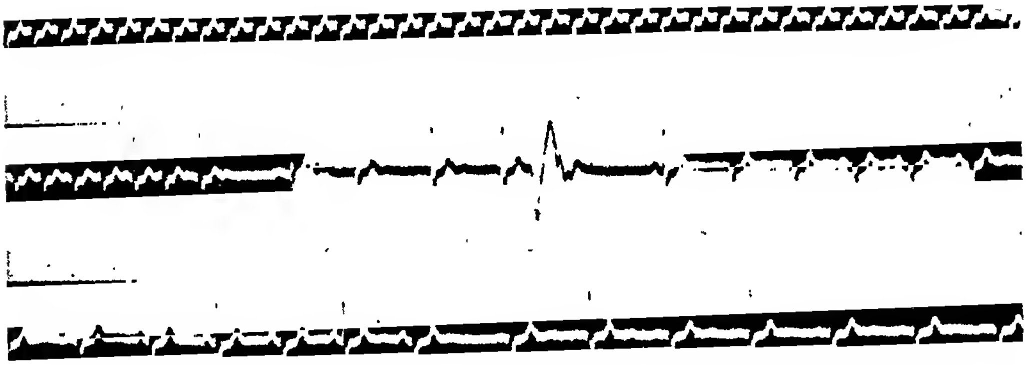

Fig. 3.—Continuous electrocardiographic record showing reversal of paroxysmal supraventricular tachycardia with Neosynephrine. Case 1, second attack.

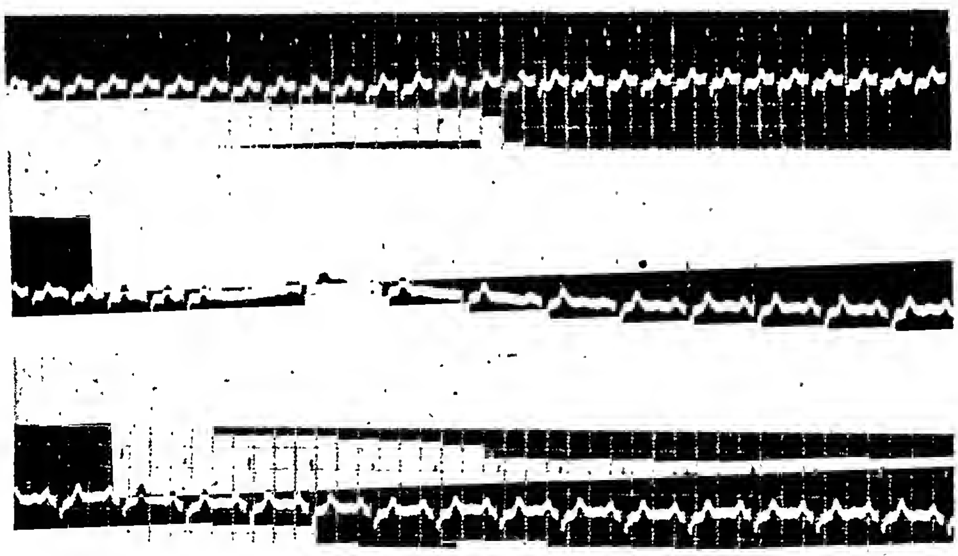

Fig. 4.—Reversal of paroxysmal supraventricular tachycardia with Neosynephrine. Case 1, third attack.

On Nov. 18, 1947, she was again seen in an attack of tachycardia. She was given, by error, 5.0 mg. of Neosynephrine intravenously! Her rhythm returned to a normal sinus mechanism in forty seconds. Sixty seconds after the injection was started, she complained of a violent headache which persisted for fifteen minutes. Her systolic blood pressure rose to 210 mm. Hg and possibly higher. Its peak was not recorded. After fifteen minutes, her pressure had returned to the preinjection level. No untoward effects other than headache were noted following this excessive dose.

Case 2.—K. H., a 51-year-old white woman, had her first attack of paroxysmal auricular tachycardia in 1911. This episode lasted fifteen minutes and terminated spontaneously. She was then free of attacks until 1941, when they recurred at a frequency of two or three per week. They were controlled with quinidine sulfate, from 90 to 180 mg. daily, and did not recur until 1943 when drug therapy was discontinued. Since 1943 she has had twelve attacks, each lasting from eight to twelve hours, and characterized by precordial pain radiating into the left arm. Her blood pressure between attacks has averaged 140/90.

On Jan. 22, 1947, she was seen in an attack which had lasted thirty-one hours and which had not responded to carotid sinus massage and ocular pressure. Mecholyl, 25 mg., likewise was ineffective and caused nausea, vomiting, and uterine cramps. Her heart rate was 165 per minute and her systolic pressure was 110 mm. of mercury. Increasing doses of Neosynephrine were given intravenously at intervals of ten minutes until the blood pressure was raised sufficiently to stop the attack. The pressure dropped to the preinjection level in each case before the next dose was given. Neosynephrine, 0.3 mg., raised the systolic pressure to 140; 0.6 mg. raised the systolic pressure to 150 mm. of mercury. No effect on the rhythm occurred. When 0.8 mg. of Neosynephrine was given intravenously, the systolic pressure rose to 160 and the tachycardia reverted to a normal sinus rhythm forty-five seconds after the beginning of the injection.

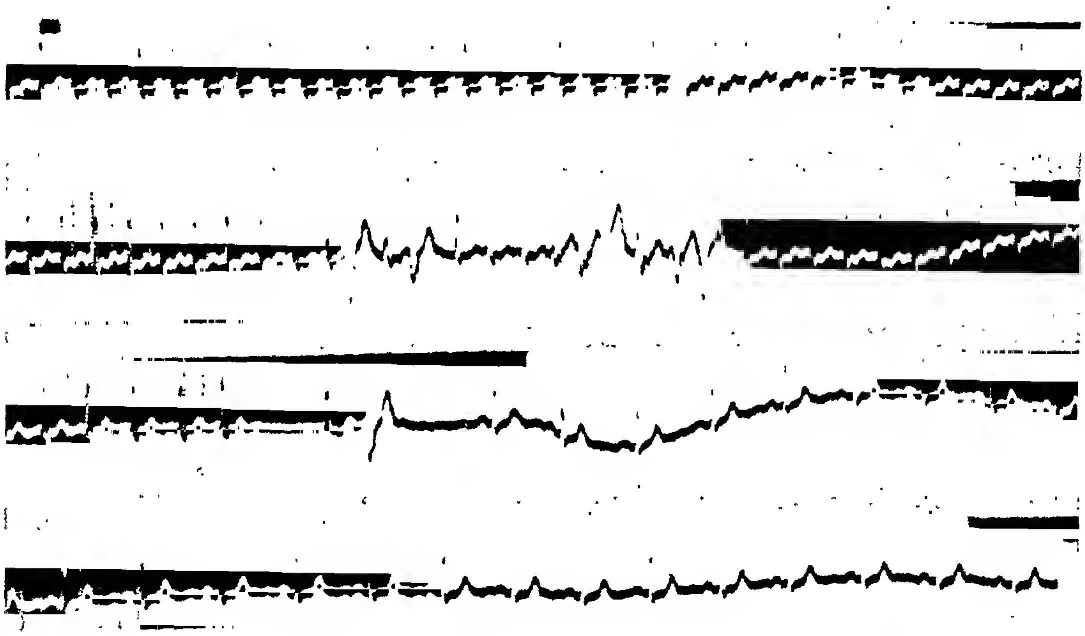

Fig. 5.—Effects of Neosynephrine on supraventricular tachycardia. Case 2, second attack. Explanations in text.

In March, 1947, she was again seen with a heart rate of 176 per minute and a blood pressure of 146/102. Neosynephrine, 0.8 mg., raised the systolic pressure to 210 in sixty seconds and caused the appearance of several ventricular beats, as illustrated in Fig. 5, but the tachycardia continued. *Neosynephrine*, 1.0 mg., raised the systolic pressure to 214 mm. Hg in seventy-one seconds, and the rhythm abruptly reverted to normal.

Case 3.—G. M., a 20-year-old white woman, had had three previous short attacks of paroxysmal tachycardia since February, 1946. On Jan. 31, 1947, she had a heart rate of 170 per minute and a systolic pressure of 110 mm. Hg which had been present four hours and persisted in spite of carotid sinus massage and ocular pressure. Electrocardiographic tracings were typical of a nodal tachycardia. Neosynephrine, 0.4 mg., intravenously, raised the systolic pressure to 140 mm. Hg and the tachycardia abruptly reverted to normal sinus rhythm forty-five seconds after the start of the injection (Fig. 6). In this instance a brief paroxysm of ventricular tachycardia preceded the reversion.

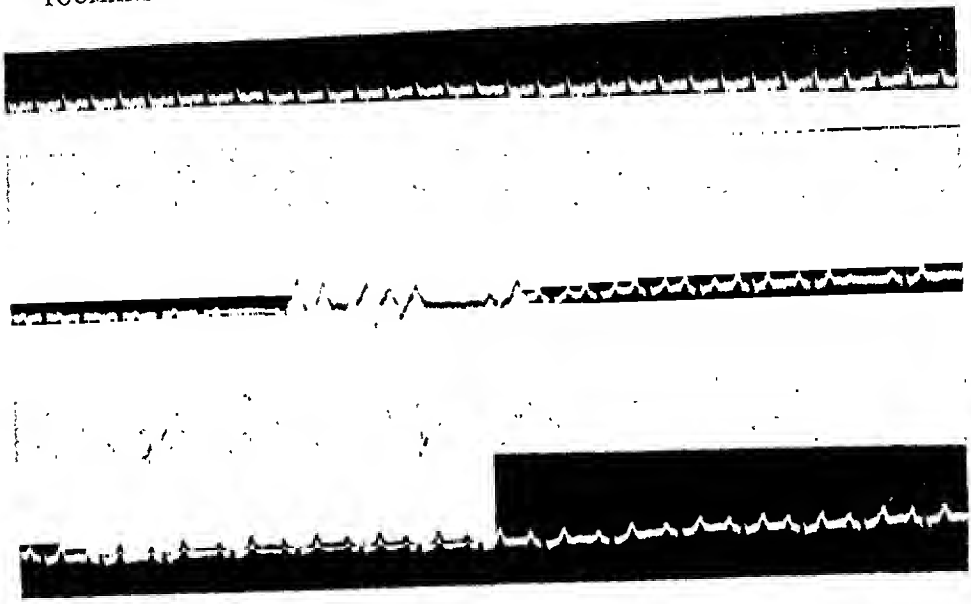

Fig. 6.—Reversal of paroxysmal supraventricular tachycardia with Neosynephrine. Case 3, first attack.

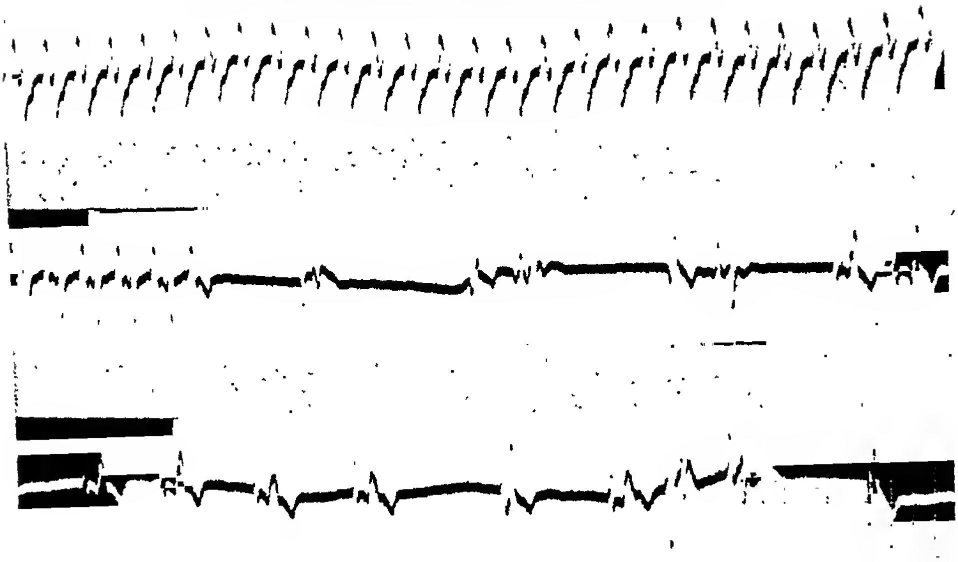

Fig. 7.—Continuous electrocardiographic record, esophageal lead, showing reversal of paroxysmal supraventricular tachycardia with Neosynephrine. Case 4, first attack.

CASE 4.—I. H., a 44-year-old white man, had had paroxysmal auricular tachycardia since 1912. In 1937 he discovered that forcing his breath against a closed glottis often abruptly terminated the attack. In 1946 his spells of tachycardia increased in frequency and were not affected by small doses of digitalis or quinidine. His normal blood pressure was 130/84.

On Feb. 13, 1947, he was seen with a heart rate of 210 and a systolic pressure of 80 mm. of mercury. The tachycardia had persisted for three days, except when it was stopped for a few minutes at a time by the Valsalva maneuver. Neosynephrine, 0.8, 1.0, and 1.2 mg., was given intravenously, in successive doses with no effect on the tachycardia. The vial from which the drug was taken was of the rubber-stoppered type, had been tapped many times, was old, and had been carried in a warm coat pocket for a number of days. A fresh glass ampule of the Neosynephrine

was obtained and 0.8 mg. of the drug from this source was injected. The systolic pressure abruptly rose from 80 to 120 mm. Hg, and the tachycardia reverted to a normal sinus rhythm forty-five seconds after the start of the injection (Fig. 7). The arrhythmia recurred again twenty minutes later. The patient was given quinidine sulfate, 180 mg. every three hours. During the next forty-eight hours he had only four attacks of tachycardia, each lasting less than one hour.

CASE 5.—P. F., a 45-year-old white woman, had had one to four attacks of paroxysmal auricular tachycardia each year since her youth. Exercise or bending over seemed to precipitate the rapid rhythm. These attacks would last only a few minutes and would terminate spontaneously when she would lie down. Her blood pressure normally was 120/70.

On Feb. 15, 1947, a hysterectomy was performed for a fibroid uterus. The hemoglobin was only 64 per cent before surgery. She tolerated the surgical procedure well, and her immediate postoperative course was uneventful. Thirty-six hours postoperatively an attack of tachycardia occurred, lasted four hours, and terminated during gaseous eructation. Two hours later tachycardia recurred, lasted five hours, and terminated spontaneously. The arrhythmia recurred for the third time at 11:00 A.M., Feb. 17, 1947. The heart rate was 180 per minute during this episode and was not affected by carotid sinus massage or ocular pressure. Beginning at 1:40 P.M., Neosynephrine was administered in increasing doses at intervals of ten minutes. The final dose of 1.9 mg. raised her systolic blood pressure from 104 to 156 and was without apparent effect on the heart rate. After four hours the attack terminated during gastric aspiration.

CASE 6.—S. G., a 53-year-old white woman, gave a history of numerous attacks of paroxysmal auricular tachycardia, the longest attack lasting five hours. Her usual blood pressure was 190/100.

On Feb. 19, 1947, during the performance of a cholecystectomy, it was noted that a ligature had been placed about the hepatic artery. The ligature was quickly removed. The artery had not been severed, and the operation was completed. When the patient left the operating table, her blood pressure was 100/70.

Twelve hours postoperatively she was observed to be in shock. Systolic blood pressure was 90. The skin was pale and cold; the heart rate was rapid, varying from 150 to 164 per minute. Because of the variability in the rate, the diagnosis of paroxysmal tachycardia was in doubt until the electrocardiogram was recorded. Neosynephrine, 0.5 mg., was given intravenously and raised the systolic pressure to 120. There was no appreciable effect on the heart rate. Five hundred cubic centimeters of plasma were administered. Shortly thereafter, 0.5 mg. of Neosynephrine raised the systolic pressure to 150, but only very slight transient slowing of the heart rate was observed. A final dose of 0.8 mg. of the drug elevated the systolic pressure to 170, but the tachycardia continued. Quinidine sulfate, 360 mg., was given rectally and repeated three hours later. One hour after the second dose, the heart rate dropped abruptly to 84 per minute, and the tachycardia did not recur.

CASE 7.—M. S., a 65-year-old white woman, had noticed attacks of paroxysmal auricular tachycardia for two and one-half years. The episodes occurred approximately two times per week and usually could be terminated by breath holding. Her blood pressure between attacks ranged from 180/110 to 218/118. Quinidine sulfate, 180 mg., twice daily, did not reduce the frequency of attacks.

On March 28, 1947, she was seen in an attack of tachycardia of six hours' duration that would not yield to the Valsalva maneuver, 180 mg. of quinidine sulfate, carotid sinus massage, or ocular pressure. The heart rate was 166 and the blood pressure was 110/80. Neosynephrine, 1.0 mg., was injected slowly over a period of three minutes, and the systolic pressure was raised to 140. This was without effect on the tachycardia. Thirty minutes later the same dose, 1.0 mg., was given rapidly in less than thirty seconds, and the tachycardia terminated sixty seconds after the start of the injection. Unfortunately, the blood pressure was not recorded at the time of the return to normal rhythm.

CASE 8.—R. R., a 55-year-old white man, suffered an attack of myocardial infarction in 1946. An episode of paroxysmal tachycardia occurred on April 27, 1947. During this attack the heart rate was 168 and the blood pressure was 94/62. The arrhythmia was not reverted by carotid

sinus massage, digitalis, or quinidine. When he was studied on May 10, 1947, his tachycardia had persisted for two weeks. He was given gradually increasing doses of Neosynephrine intravenously. The largest dose was 2.0 mg. and raised the systolic blood pressure only to 130 mm. of mercury. No change in the rhythm was observed on the electrocardiogram. Subsequently it was shown by the use of an esophageal lead that the tachycardia was ventricular in character (Fig. 8).

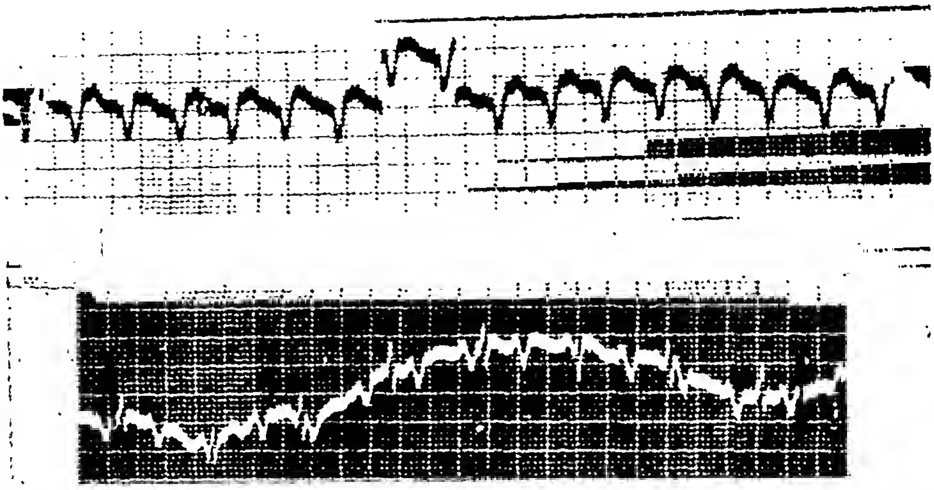

Fig. 8.—Case 8. Ventricular tachycardia. Upper record shows Lead I in which P waves are obscured; therefore, the arrhythmia could be interpreted either as a ventricular tachycardia or as a supraventricular tachycardia with a ventricular conduction defect. Lower record is from an esophageal lead which clearly shows a ventricular rate of 168 and an auricular rate of 96.

CASE 9.—A. B., a 59-year-old white woman, had noted paroxysmal auricular tachycardia since the age of 18 years. The attacks occurred rarely at first but had increased to two per month since 1944. Frequently during attacks she had precordial pain radiating to the left shoulder and arm; this pain had been treated freely with nitroglycerin.

On May 26, 1947, she was seen within an hour after the onset of tachycardia. The heart rate was 160 per minute and the systolic blood pressure was 76. Her usual blood pressure was 110/68. Neosynephrine, 10 mg., was injected intravenously. This excessive dose was the result of a miscalculation. Marked pain in the head and back of the neck occurred, and this was associated with severe agitation. The blood pressure was not recorded. The electrocardiogram showed a brief period of asystole, then numerous ectopic ventricular systoles superimposed on a sinus bradycardia. After ten minutes there was a regular sinus rhythm with a rate of 60 beats per minute.

CASE 10.—A. W., a 28-year-old white man with tuberculosis of the lungs and spine and a tracheomediastinocutaneous fistula, had experienced one episode per month of paroxysmal auricular tachycardia since February, 1946. The attacks lasted from fifteen minutes to several hours and previously had responded to carotid sinus massage. His usual blood pressure ranged from 110/70 to 120/76. In March, 1947, he was digitalized without significant reduction of the frequency of attacks.

On July 12, 1947, he had a heart rate of 170 and a blood pressure of 96/70. This attack had persisted for six hours in spite of repeated attempts to stop it with carotid sinus massage and ocular pressure. Neosynephrine, 0.5 mg., elevated his blood pressure to 142/92 and his tachycardia abruptly terminated thirty seconds after the beginning of the injection. Quinidine sulfate, 180 mg., three times per day, was started and digitalis was discontinued.

On July 30, 1947, another attack began at 4:00 A.M. The heart rate was 168 and the blood pressure was 84/64. At 7:00 A.M. Neosynephrine, 0.5 mg., raised his blood pressure to 136/86

and normal sinus rhythm was restored forty-five seconds after the start of the injection. On Aug. 13, 1947, at 2:00 P.M. an attack of paroxysmal auricular tachycardia again responded to Neo-synephrine, 0.5 mg., which elevated the blood pressure to 133/96 in sixty-two seconds.

Two recurrences on October 16 and October 23 would not respond to carotid sinus massage and were terminated by 0.5 mg. of Neosynephrine. Quinidine sulfate, 180 mg., three times per day, had been maintained since July 12.

DISCUSSION

Degree of Rise in Blood Pressure Required to Revert Tachycardia to Sinus Rhythm.—The extent of the rise in blood pressure produced by intravenous Neosynephrine is variable. A dose of 0.5 mg. is a suitable initial trial dose in the typical case. This amount will in some cases terminate the arrhythmia; in others it is insufficient but will serve to assay the patient's pressor response to Neosynephrine. In some of the cases the rhythm was reverted to normal by only enough Neosynephrine to increase the blood pressure suddenly from the subnormal level seen during the attack up to the patient's normal level. This suggests that, in such cases, the low blood pressure secondary to the tachycardia may be an important factor in the perpetuation of the attack. In Case 2 it was necessary to increase the systolic blood pressure to above 200 mm. Hg to stop the arrhythmia. In this case mechanical measures and Mecholyl (25 mg. subcutaneously) were unsuccessful. In Case 1 the doses of Neosynephrine used in the treatment of the first two attacks were greater than necessary, and although the systolic pressure rose to over 200 mm. Hg, the arrhythmia reverted when the systolic pressure reached 160 mm. of mercury. Thus, twelve of the nineteen attacks treated were reverted at a systolic pressure of 160 mm. Hg or less. In two of the cases, data concerning the maximal systolic pressures produced were not obtained. In Case 9, by mistake, twenty times the proper initial dose was given. The paroxysmal auricular tachycardia reverted to ventricular bradycardia and then shortly returned to a normal sinus rhythm. Fortunately, no serious effects resulted.

Time of Reversion.—In each case a suitable amount of Neosynephrine was diluted so that it could be injected conveniently in a period of twenty to thirty seconds. The appearance of normal sinus rhythm occurred during the period of thirty-five to seventy seconds from the beginning of the injection during the time when the systolic blood pressure was rapidly rising.

If reversion of the tachycardia does not occur after a given dose of Neosynephrine, a larger dose may be used any time after the blood pressure has returned to the preinjection level. This has required not longer than ten minutes in the cases studied.

Side Effects.—Amounts of Neosynephrine which are sufficient in the majority of cases to revert paroxysmal supraventricular tachycardia to normal sinus rhythm produce no unpleasant symptoms. "Tingling" or "coolness" of the skin have been noted by most of the patients. Presumably, this is due to the cutaneous vasoconstriction and pilo-erection. A sensation of "fullness of the head" may be produced, and headache may be caused by excessive doses. Transitory pre-

cordial pain has been noted following moderate doses in patients who have complained previously of this symptom during attacks of tachycardia.

Effects in Refractory Cases.—Most of the attacks reverted by Neosynephrine had failed to respond to carotid sinus massage or to ocular pressure. Some of the attacks had persisted in spite of large doses of Mecholyl. The only failures with Neosynephrine were in two patients who developed attacks postoperatively. In Case 5 the maximum systolic pressure produced was 156 mm. Hg; it is quite possible that a larger dose would have reverted the attack. In Case 6 an increase in the pressor action of Neosynephrine after the blood volume was increased by the administration of plasma was demonstrated. A maximal systolic pressure of 170 mm. Hg was produced without affecting the arrhythmia. However, this patient normally had a blood pressure of 190/100, and it is possible that restoration of this level would have resulted in reversion.

Conditions Altering the Cardioinhibitory Response to Neosynephrine.—As would be expected, Neosynephrine is less effective as a pressor agent when the blood volume is low. This was observed in one of our cases when the same dose of Neosynephrine was given before and after transfusion. Doses of Neosynephrine as high as 5.0 mg. have been given intravenously to patients in shock,[5] and the only response noted was minor elevation in blood pressure. It appears that the maximal dose of Neosynephrine which can be given safely is determined by the degree of rise in blood pressure. It is to be expected that Neosynephrine will not revert paroxysmal tachycardia in the occasional cases in which it fails significantly to elevate the blood pressure.

The pressor action of Neosynephrine may be counteracted by previous administration of vasodilator drugs. Adrenolytic drugs would be expected to block its vasoconstrictor action. Heavy doses of barbiturates produce vasodilatation and decrease the sensitivity of the carotid sinus reflexes. Some drugs, such as morphine and neostigmine, sensitize carotid sinus cardioinhibitory reflexes. Therefore, previous administration of these drugs would not be expected to interfere and might increase the effectiveness of Neosynephrine in paroxysmal supraventricular tachycardia. It is obvious that the effects of Neosynephrine cannot be evaluated adequately when the patient is under the influence of various other drugs.

Relative Contraindications to Neosynephrine.—The doses of Neosynephrine which are used to revert paroxysmal supraventricular tachycardia frequently produce ventricular extrasystoles, and occasionally produce a brief paroxysm of ventricular tachycardia at the time of the reversion. Large doses of the drug have a direct stimulatory action on the ventricles, but the extrasystoles seen with small doses may be on a ventricular escape basis or they may, perhaps, be initiated by the sudden change in pressure in the ventricles. We have seen, in experimental animals, that various pressor compounds produce extrasystoles during the rise in blood pressure, even though some of the compounds, such as Pitressin, have no direct stimulatory action on the ventricles. Moreover, huge doses of Neosynephrine do not produce ventricular fibrillation in dogs. However, an increased ventricular irritability may, perhaps, be considered as constituting a

relative contraindication to the use of Neosynephrine intravenously; and, since cardioinhibitory reflexes may not be utilized to influence a ventricular focus, there is less rationale for the use of Neosynephrine in the treatment of ventricular tachycardia. The possibility may be considered that in an occasional instance ventricular tachycardia could be caused by a local effect of sympathetic activity and that this activity could be reflexly depressed following Neosynephrine injection. In this study it was given to one patient with ventricular tachycardia (Case 8). A dose of 2.0 mg. did not produce the expected degree of rise in the blood pressure, and there was no effect on the arrhythmia. In view of the facts just stated, as a general rule the supraventricular origin of the tachycardia should be established before Neosynephrine is used.

A ventricular conduction defect not infrequently becomes evident during an attack of paroxysmal supraventricular tachycardia. When only the standard leads are used in such cases, the electrocardiographic record may resemble that seen in ventricular tachycardia. The differentiation between the two types of arrhythmia can be made by the use of an esophageal lead in which the large auricular deflections are more easily identified.[6] Records obtained by esophageal leads are illustrated in Fig. 7 and the lower portion of Fig. 8.

The presence of hypertension during the tachycardia, or evidence of considerable impairment of coronary circulation, may also be considered as relative contraindications to the use of Neosynephrine intravenously.

SUMMARY

Neosynephrine restores the normal sinus rhythm within thirty-five to seventy seconds after rapid intravenous injection in most cases of paroxysmal supraventricular tachycardia. The reversion of the supraventricular tachycardia is attributable to reflex cardiac inhibition elicited by the rapid rise in pressure in the carotid sinuses and aortic arch. The rise in pressure occurs as a result of the vasoconstriction produced by Neosynephrine. Presumably, any vasoconstrictor compound which acts quickly and briefly, and which has little or no direct stimulating action on the cardiac conducting system, would revert paroxysmal supraventricular tachycardia.

Neosynephrine reverted paroxysmal supraventricular tachycardia in most cases when the systolic pressure reached a level of 160 mm. Hg or less. Some of the attacks which were terminated were refractory to treatment by mechanical methods and by various drugs. In occasional cases reversion was produced with Neosynephrine only when the systolic pressure was elevated to levels which might be considered too high for safety.

In the typical case the rise in systolic blood pressure is proportional to the dose of Neosynephrine, and the maximum dose to be used is determined by the maximum rise in pressure which is considered safe for the individual patient. The initial dose should not exceed 0.5 mg., and any subsequent dose is selected on the basis of the pressor response to the initial dose. Most attacks were reverted by 1.0 mg. or less.

These studies suggest that intravenous injection of Neosynephrine, or some other rapid-acting vasopressor substance, will prove to be the treatment of choice in selected cases of paroxysmal supraventricular tachycardia.

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lateral infarct were analyzed previously,[4] whereas those referable to the primary lateral infarct will be considered in this communication. Eight patients (Cases 142, 145, 151, 152, 154, 157, 158, and 159) who had primary lateral infarcts that continued into the posterolateral wall were mentioned in summary of the findings in posterolateral infarction,[5] but will receive detailed consideration herein.

The present study, therefore, has been narrowed to twenty-seven patients with primary lateral infarction which at autopsy was confined to, or located principally in the lateral wall of the left ventricle. Twenty-four of these cases (Cases 138 *through* 161) will be reported in detail and the remainder (Cases 4, 17, and 60) have been reported in previous communications because of infarction elsewhere in the heart, but will be included in the discussion.

CASE REPORTS

CASE 138.—A 55-year-old man had been in good health until February, 1944, when he began to have typical angina pectoris. On March 9, 1944, he was seized suddenly with an exceptionally severe attack which resulted in syncope. After consciousness returned, the pain was still present and persisted until relieved by morphine. There were classical physical signs of aortic stenosis and laboratory findings compatible with recent myocardial infarction. On March 19 the patient was suddenly seized with extreme dyspnea, accompanied by circulatory collapse, but not by pain. He recovered from this attack, but died suddenly on March 24. No cardiac glycosides were given.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 1,*A* were obtained on March 10, twelve hours after the onset of the thoracic pain and syncope, on March 11, and on March 22, two days before death. The initial phase of the QRS complex was consistently upright in all precordial leads and in the standard limb leads. However, Lead aV_L, which is not reproduced, showed an initial Q wave 1.0 mm. in depth and 20 per cent of the succeeding R wave, followed by a diphasic T wave of low voltage. This finding was consistent with left ventricular hypertrophy and was not considered diagnostic of infarction. The tall R waves in Leads V_6 and V_6 with slurred ascending limbs of 0.04 second duration and the deep S waves of Leads V_1 and V_2 were also strongly suggestive of left ventricular hypertrophy. The R waves of Leads V_5 and V_6 of the second tracing were almost identical in amplitude and configuration with those of the first tracing and the R waves in the same leads of the final electrocardiogram showed a 33 per cent reduction in voltage without alteration in contour. The variations in the QRS pattern in Leads V_3 and V_4 were transitional in type and were attributable to shift in the position of the electrode in reference to the interventricular septum. The most striking change in the serial electrocardiograms took place in the RS-T segment and T wave of the last four precordial leads (V_3 through V_6). In the tracing of March 10 there was an abnormal depression of the RS-T segment in the last three precordial leads, which amounted to 2.0 mm. in V_4 and 1.0 mm. in V_5 and V_6. The following day the RS-T depression had become considerably greater, especially in V_5 and V_6, and the terminal upright portion of the T wave had decreased significantly in amplitude. The Q-T interval was abnormally long. In the final tracing, the RS-T segment was still depressed in Leads V_4, V_5, and V_6, but had changed considerably in contour as a result of the reversal in the direction of the T wave, which had become sharply inverted, not only in these leads, but also in transitional Lead V_3. These changes in the RS-T segment and T wave were comparable to those described by Wood, Wolferth, and Bellet as characteristic of lateral infarction.[8] As mentioned in the history, this patient received no cardiac glycosides or quinidine, so that drug effects could be excluded positively. The differential diagnosis rested between a patchy infarct of the subendocardial aspect of the anterolateral wall of the apex and acute ischemia in the same area. The absence of Q waves was more in keeping with the latter, but did not positively exclude a subendocardial infarct.

Pathologic Findings.—The heart weighed 523 grams as a result of left ventricular hypertrophy secondary to rheumatic aortic stenosis. An organizing infarct of two to three weeks'

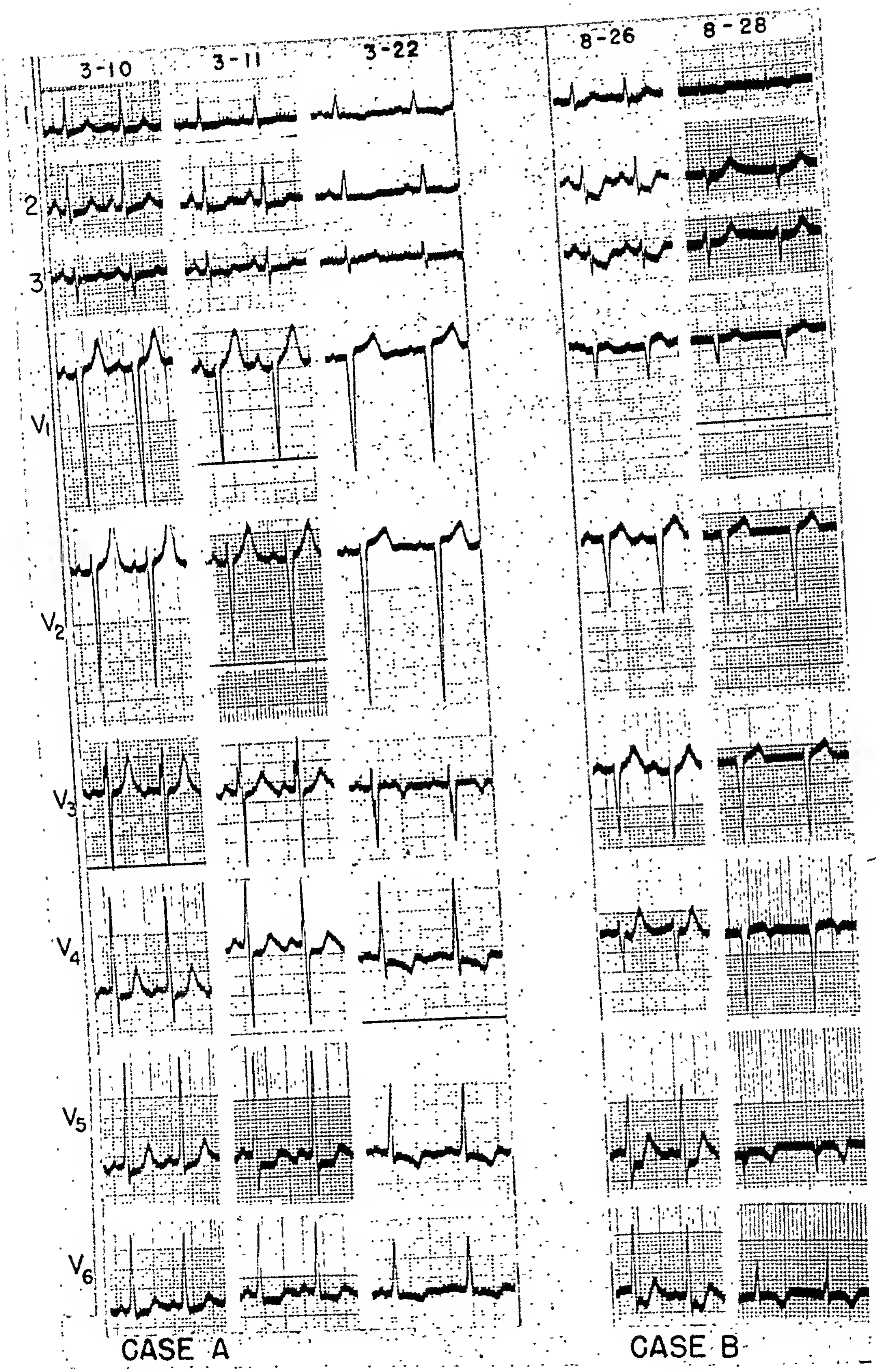

Fig. 1.—Serial electrocardiograms during acute infarction of the anterolateral aspect of the apex. *A*, Case 138; *B*, Case 139.

duration was found in the anterolateral aspect of the left apex, as demarcated by the solid lines of Fig. 2. Upon microscopic examination, the lesion was confined to the subendocardial one-half of the lateral aspect of the apex and was found chiefly in the mid-zone of the anteroapical wall, but extended in fingerlike fashion to the endocardial surface. The subepicardial one-half of the anterolateral wall was not infarcted. There was good correspondence between the serial changes in RS-T segment and T wave and the organizing infarct limited to the subendocardial one-half of the anterolateral wall of the apex. The absence of Q waves may have been due to the relatively small size and patchy character of the subendocardial infarct, but the voltage of the R waves in Leads V_4, V_5, and V_6 was greater than would have been expected in the presence of such a lesion. In view of the autopsy findings, it is possible that the one-third reduction in the voltage of the R wave in Leads V_5 and V_6 of the final tracing may have been significant.

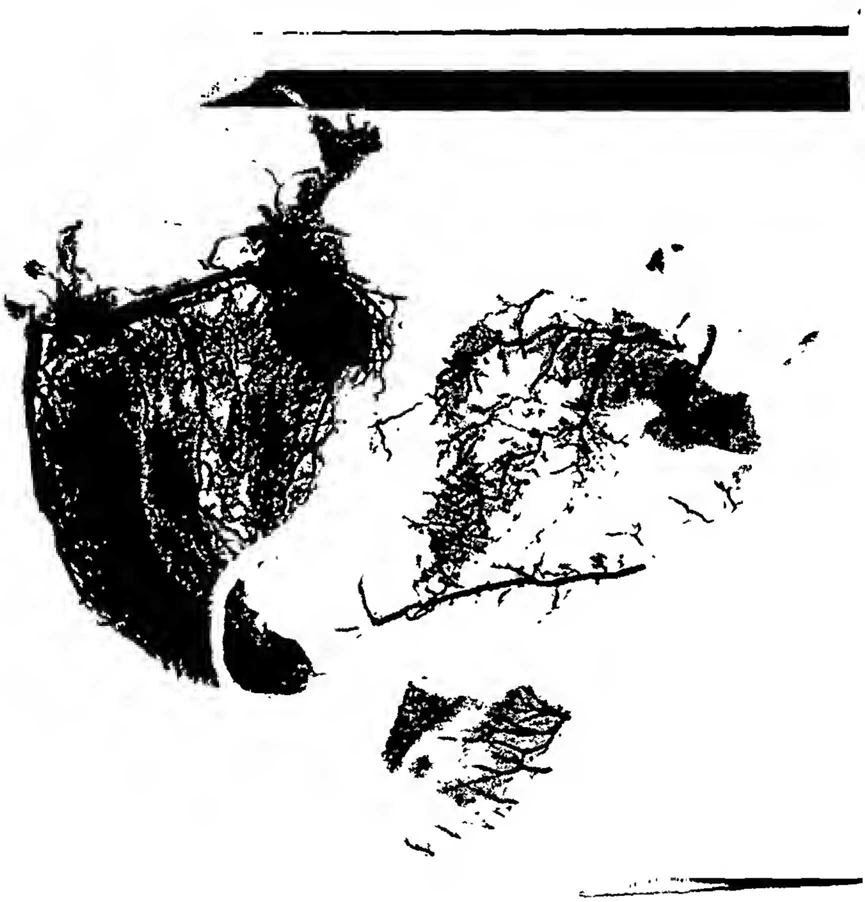

Fig. 2.—Roentgenogram of the injected heart in Case 138.

Case 139.—A 59-year-old man had been perfectly well up until June, 1944, when he began to notice exertional and paroxysmal nocturnal dyspnea. On August 24 and 25 he had several transient attacks of retrosternal oppression, provoked by exercise and promptly relieved by rest. At noon on August 26 he was seized with severe, crushing retrosternal pain which radiated down the inner aspect of the right arm and led to admission in circulatory collapse three and one-half hours later. The pain was relieved by morphine, but returned early in the morning of the 28th and persisted in spite of further opiates. Death occurred forty-nine hours after admission. No cardiac glycosides were administered prior to or during hospitalization.

Electrocardiographic Findings.—Electrocardiograms obtained at 4:30 P. M. on August 26 and at noon on August 28 are reproduced in Fig. 1,*B*. The first electrocardiogram, taken four and one-half hours after the onset of the pain, was comparable to the original tracing in Case 138.

The initial phase of the QRS complex was upright in all precordial leads except V_1, where there was a QS complex. The QS deflection in V_1 and the minute initial R wave of V_2 and V_3 were within the limits of normal variation. The electrode at precordial Position 4 was near the transitional zone, whereas that at Positions 5 and 6 reflected the potential variations of the anterolateral aspect of the left ventricle. The striking feature of the precordial leads was the 2.0 mm. depression of the RS-T segment in Leads V_5 and V_6. This depression could not have been reciprocal to a transmural posterior infarct, since Leads aV_F, II, and III showed an RS complex with a 2.0 mm. RS-T depression comparable to that in V_5 and V_6. Digitalis effects were excluded positively from the history. The differential diagnosis lay between an acute ischemia of the subendocardial portion of the anterolateral and posterior aspects of the apex and a patchy subendocardial infarct in the same location. The absence of Q waves was in favor of the former, but did not exclude the latter. Lead aV_L showed a normal R wave, an isoelectric RS-T junction, and upright T wave, and was apparently reflecting the potential variations of a portion of the lateral wall of the left ventricle basal to the lesion. A study of the tracing of August 28 revealed striking changes in the QRS complex of the last three precordial leads, particularly of V_5. The formerly tall R wave in this lead was reduced to 1.0 mm. and was preceded by an abnormal Q wave 5.0 to 6.0 mm. deep. The formerly tall, upright T wave had become sharply inverted and the RS-T segment had become isoelectric. The changes in the QRS deflection in Lead V_5 were pathognomonic of incomplete transmural infarction of the anterolateral wall of the left apex, and the changes in the RS-T compex and T wave in this lead signified that the lesion which formerly had been limited to the subendocardial portion of the wall had extended to involve the subepicardial layer of muscle. In Lead V_4 the initial R wave almost disappeared, the RS-T junction became isoelectric, and the RS-T segment and T wave reversed in direction. In view of the findings in Lead V_5, those in V_4 were interpreted as indicating that the original subendocardial lesion had extended in patchy fashion through the anteroseptal portion of the left apex. The initial upright deflection in Lead V_6 persisted, but was reduced to 50 per cent of its former amplitude. The RS-T junction in this lead became isoelectric and the T wave exhibited sharp cove-like inversion. These changes were due most likely to extension of the lesion in patchy fashion through the lateral aspect of the apex, but might have been the result of infarction confined to the subepicardial one-half of this region. Comparable changes occurred in the R wave and T wave of Lead I. The formerly depressed RS-T segments in Leads II and III became isoelectric and the T waves became tall, upright, and reciprocal in contour to those of V_5 and V_6. Unfortunately, Lead aV_F was not obtained on August 28. The changes in standard Leads II and III were due most likely to a disappearance of the ischemia of the subendocardial portion of the posterior wall together with the development of reciprocal effects from the acute infarct of the anterolateral aspect of the apex.

Pathologic Findings.—The heart weighed 500 grams and revealed an acute infarct of the anterolateral wall of the apex, almost identical in position with that in Case 138 (Fig. 2), except for the absence of the knoblike extension toward the posterior wall. On microscopic examination, the infarct was estimated to be one to two days old. It involved principally the subendocardial one-half of the wall, but exhibited fingerlike projections to the epicardium together with a complicating pericarditis. The findings at autopsy thus confirmed the position and character of the infarct, as predicted from the QRS-T pattern in the tracing of August 28. The status of the lesion at the time of the first electrocardiogram, made four and one-half hours after the onset of symptoms and forty-eight hours before death, was left unsettled. On the basis of the histologic findings, it was impossible to reach a positive conclusion as to whether the lesion found at autopsy had commenced before or after the time of the first electrocardiogram. Judging from the profound circulatory collapse, it seemed likely that the subendocardial lesion found at autopsy had begun prior to admission. If so, the marked RS-T segment depression in Leads V_4 through V_6 constituted the earliest manifestation of a developing subendocardial infarct, and the concurrent registration of a normal initial R wave in these leads was best explained by the assumption that the degenerative changes were not sufficiently advanced to have prevented the response to the activating impulse. However, it is conceivable that the lesion at the first electrocardiogram consisted merely of subendocardial ischemia and that the histochemical changes of anterolateral infarction developed subsequently. Since the posterior wall of the apex was negative histologically, the

transient RS-T segment depression in Leads II and III was apparently the result of a transient ischemia of the posterior aspect of the apex.

CASE 140.—A 65-year-old man was brought to the hospital four hours after the sudden onset of constrictive retrosternal pain which radiated down the left arm and was accompanied by severe dyspnea. Death occurred thirty-one hours after admission. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram was obtained twelve hours after admission, but is not reproduced because of its resemblance to the last tracing (March 22) in Case 138 (Fig. 1,*A*). There was no significant difference in the QRS pattern in the first four precordial leads of the two patients. Comparison of Leads V_5 and V_6 of this patient with those of the electrocardiogram of March 22 (Fig. 1,*A*) revealed that the R wave was only about two-thirds as tall and was preceded by a minute Q wave, whereas the depressed RS-T segment and inverted T wave were similar in contour. The QRS-T pattern in the standard leads was similar in the two cases, except that the R wave of Lead I in this case was coarsely notched and only one-half as tall. In Lead aV_L in this case there was coarse notching of the upstroke of the R wave, an isoelectric RS-T junction, and a sharply inverted T wave. The findings in Leads V_5, V_6, and aV_L might have been due to ischemia or patchy infarction of the subendocardial layer of the anterolateral wall or merely to uncomplicated left ventricular hypertrophy. For a positive differentiation, further tracings would have been required, but were not obtained because of the early death of the patient.

Pathologic Findings.—The heart weighed 460 grams and revealed a recent small infarct in the anterolateral wall of the apex, comparable in size and position to that in Case 138 (Fig.2), except for the lack of the knoblike projection toward the posterior wall. This infarct was mainly in the mid-zone at the apex and became subendocardial near its upper border in the anterolateral wall. The patchy character and relatively small size of the infarct probably accounted for the lack of abnormal Q waves. The RS-T depression and inverted T waves of Leads V_5 and V_6 could be correlated with involvement of the subendocardial and mid-zones and sparing of the subepicardial layer.

CASE 141.—A 46-year-old man had noticed gradually increasing exertional dyspnea since 1938 and paroxysmal nocturnal dyspnea since 1941. He gave no history of chest pain until Nov. 23, 1943, when he had two brief attacks of mild retrosternal constriction. On Dec. 10, 1943, he was seized with a vise-like retrosternal pain, which lasted until morphine was given on hospitalization five hours later. Because of refractory congestive failure, digitalis was started on Jan. 24, 1944, and given in a dose of 0.2 Gm. daily until February 5. Severe retrosternal pain recurred on January 30. A pericardial friction rub was heard at the apex on February 5 and persisted until his death on February 12.

Electrocardiographic Findings.—Electrocardiograms selected from a series during his two months' hospital stay are reproduced in Fig. 3. The initial tracing, taken on Dec. 11, twenty hours after the onset of the pain, revealed signs typical of a large anterolateral infarction, namely, a distinct initial R wave in V_1, a questionable initial R wave in V_2, a QS complex, elevated RS-T junction and cove-shaped inversion of the T wave in V_3, and an abnormal QR complex with elevated RS-T junction and typical "coronary" T wave in Leads V_4, V_5, V_6, and aV_L. The deep Q wave of Lead aV_L was practically obliterated from Lead I because of the concurrent initial negativity of the right arm. In succeeding tracings an initial R wave, deep S wave, slightly elevated RS-T junction, and normal upright T wave were consistently found in Leads V_2 and V_3 and a QS complex appeared in V_4. The RS-T segments and T waves in Leads V_4, V_5, and V_6 showed the usual evolution until January 28, when there was a recurrence of the upward displacement of the RS-T junction. The RS-T segment elevation became more marked on February 4, which was the first tracing taken after the second attack of severe retrosternal pain. These changes indicated further injury to the subepicardial aspect of the anterolateral wall of the left ventricle and could have been due to reinfarction or to intercurrent pericarditis.

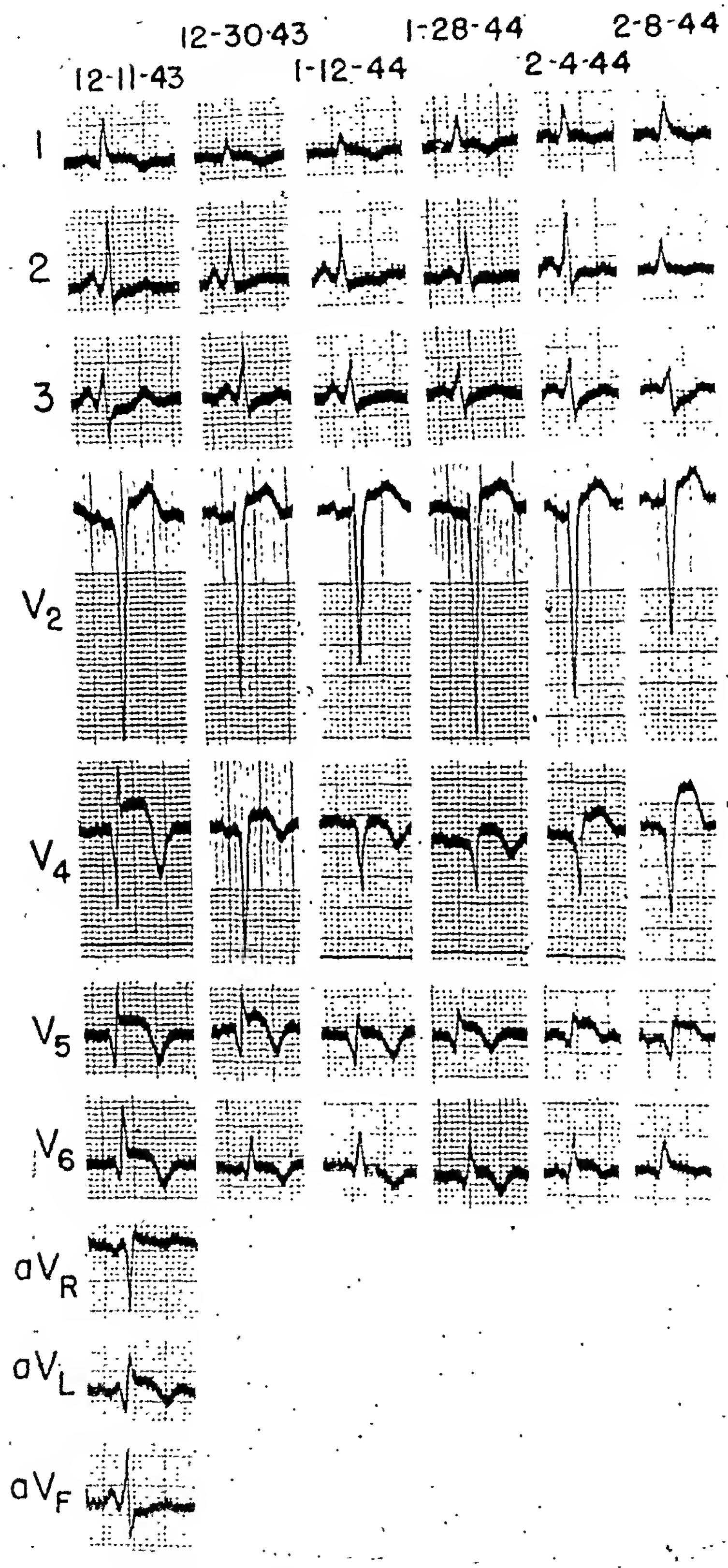

Fig. 3.—Serial electrocardiograms in Case 141.

Pathologic Findings.—The heart weighed 501 grams and exhibited an organizing infarct, occupying most of the apical two-thirds of the lateral aspect of the left ventricle, as demarcated by the solid line of Fig. 4. In its thinnest portion the lateral wall was 3.0 mm. in thickness. Microscopic examination showed an organizing infarct, extending patchily from endocardium to epicardium with a recent reinfarction one to two weeks old affecting the portions of the subepicardial muscle which had been spared in the first attack. Although this infarct did not reach the junction of the anterior wall and septum, it apparently extended far enough into the anterior wall to produce classical findings in Lead V_4. The QR patterns in Leads V_5 and V_6 corresponded quite well with the involvement of the anterolateral and lateral walls of the left ventricle, and those in V_1, V_2, and V_3 of all tracings made subsequent to December 11 corresponded with the sparing of the anteroseptal wall of the left ventricle. The transient abnormality in the initial phase of the QRS complex noted only in the first tracing may have been due to early injury to the anteroseptal wall with subsequent spontaneous reversal. The increased RS-T segment elevation in the last two tracings reflected injury to the subepicardial muscle consequent upon the reinfarction found at autopsy.

Fig. 4.—Roentgenogram of the injected heart in Case 141, showing large lateral infarct.

CASE 142.—A 46-year-old man was admitted to the hospital with a history of dyspnea, cough, hemoptysis, right-sided pleural pain, and fever of two weeks' duration. No definite history of myocardial infarction could be elicited. Physical examination revealed congestive failure complicated by bronchopneumonia. Although the pneumonia resolved, decompensation persisted, ending in death on the fifteenth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained six hours after admission and before the administration of cardiac glycosides is reproduced in Fig. 5,*A*. The initial phase of the QRS complex was upright in the first four precordial leads and measured 4.0 mm. in V_1 and 5.0 mm. in V_2, and then fell off to 3.0 mm. in V_3 and to 2.0 mm. in V_4. The abnormal QR complexes in Leads V_5 and V_6 were considered diagnostic of infarction and the T waves in these leads suggested an old, rather than a recent, lesion. In Lead aV_L there was a relatively deep Q wave and a small late R wave suggestive of infarction. Because of the inversion of the P wave in Lead

aV_L, it was necessary to consider transmission of potential variations of the left atrium to the arm as an alternative explanation for the QR pattern in aV_L.[11,12] However, in subsequent tracings taken in the sitting position, an abnormal QR pattern was recorded in aV_L in association with an upright P wave. This was interpreted as evidence that the findings in Lead aV_L were due to

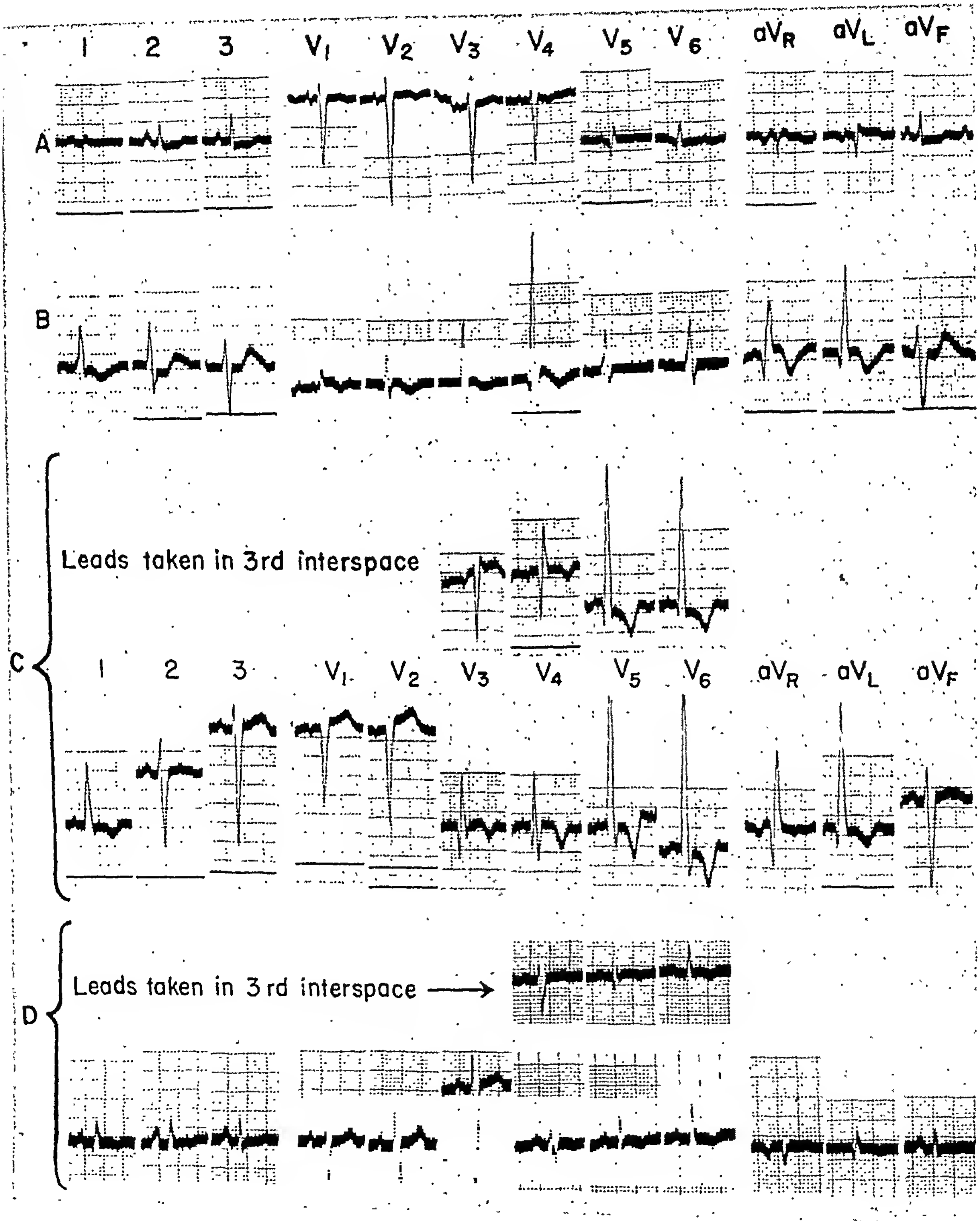

Fig. 5.—Electrocardiograms in lateral infarction. *A*, Case 142; *B*, Case 143; *C*, Case 144; *D*, Case 145.

lateral infarction. The abnormal QR complex of aV_L tended to carry over into Lead I, but the Q wave was greatly reduced in amplitude because of the concurrent negativity of the right arm. Thus, the QR pattern in Lead I was not as abnormal as that in aV_L. The elevation of the RS-T junction and monophasic upright T wave in aV_L of the first tracing, together with the reciprocal depression of the RS-T segment in aV_F, was suggestive of recent lateral infarction, and the subsequent return of the RS-T junction to the isoelectric line constituted further supportive evidence. On the other hand, the T wave in aV_L, V_5, V_6, and Lead I failed to undergo the cove-like inversion typical of organizing infarct. Thus, the age of the lateral infarct remained in doubt.

Fig. 6.—Roentgenogram of the injected heart in Case 142, showing large, recent lateral infarct in solid outline and old, healed anteroseptal infarct in broken lines.

Pathologic Findings.—The heart weighed 388 grams and revealed an organizing lateral infarct, demarcated by the solid lines of Fig. 6, and an old, completely healed infarct, which involved the apical one-half of the anteroseptal wall and extended slightly into the lateral wall at the tip of the apex, as indicated by the broken lines of Fig. 6. There was moderate right ventricular dilatation, apparently due to the combination of the left heart failure and pneumonia. After a review of the electrocardiograms in the light of the autopsy findings, it was concluded that the right ventricular dilatation was responsible for the RS pattern in the first four precordial leads and that the transitional zone was between Positions 4 and 5. This right ventricular dilatation could have produced sufficient clockwise rotation of the heart to cause transmission of the potential variations of the anteroseptal aspect of the left ventricle to the axilla instead of to Positions 3 and 4. The old healed anteroseptal infarct was considered the more likely cause of the abnormal QR pattern in Leads V_5 and V_6 than the recent lateral infarct because of the absence of the characteristic serial changes in the RS-T segment and T wave from these leads The fact that the RS-T segment was originally elevated in Lead aV_L and reciprocally depressed in aV_F and subsequently isoelectric in both leads suggested that the pattern in aV_L was produced by the recent high lateral infarction. Although this infarct extended into the posterolateral wall near the apex, characteristic changes were not produced in Lead aV_F.

CASE 143.—A 63-year-old woman was brought to the hospital in coma complicated by profound circulatory collapse. No further history was obtainable. Death occurred one hour after admission. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained one-half hour after admission is reproduced in Fig. 5,*B*. Interference dissociation was present with an atrial rate of 70 and a regular ventricular rate of 90 per minute. The ventricular complexes were uniform in any given lead and thus arose from a single focus. The following interpretation was based on the supposition of a nodal, rather than idoventricular, pacemaker. The duration of the QRS complex was 0.12 second and abnormal slurring or notching was present in every lead except V_3. An initial Q wave was recorded in Leads V_1, V_2, and V_4, but was absent from most cycles of Lead V_3, probably because the first portion of the QRS complex was isoelectric in this lead. This assumption was supported by the fact that the measurable QRS duration in V_3 was only 0.08 second, as compared with 0.12 second in leads to the right and left. The Q wave of Lead V_1 was followed by a notched upstroke, late intrinsicoid deflection, elevated RS-T junction, and coved inversion of the T wave. Lead aV_R also displayed a Q wave, prominent late R wave, elevated RS-T junction, and deeply inverted T wave. The findings in Leads V_1 and aV_R were subject to two widely divergent explanations: (1) anteroseptal infarction, involving enough of the septum to produce the pattern of right bundle branch block in Leads V_1 and aV_R and continuing sufficiently into the subendocardial portion of the anterior wall to account for the Q wave in Lead V_4; (2) rotation of the heart, so that the potential variations of the posterobasal aspect of the left ventricle were transmitted to the right arm and carried through to the right anterior chest wall to produce the QR pattern in V_1. It was difficult to reconcile the second alternative with the fact that the transitional zone was apparently near the midline anteriorly and the potential variations of the anterior and lateral walls of the left ventricle were referred to precordial Positions 2 to 6, inclusive. This would have meant that the potential variations of some portion of the epicardial surface of the left ventricle would have been referred around the entire circumference of the chest, which was anatomically implausible. Hence, the first alternative was favored. The pattern in Leads V_2 and V_3 was subject to slight cyclic variation, a minute initial Q wave usually being present in V_2 and absent from V_3, but in a minority of cycles the Q wave was absent from V_2 and present in V_3. A Q wave was consistently present in Lead V_4 and varied from 2.0 to 4.0 mm. in depth and from 5 to 10 per cent of the amplitude of the succeeding R wave. Despite the low Q/R ratio, the Q wave was considered abnormal because of its coarse slurring and because of the 0.04 second interval from its onset to nadir. This, together with the RS-T elevation and T-wave inversion, pointed to a recent patchy infarct. Leads V_5 and V_6 showed an initial upstroke that was abnormally slurred and prolonged. The pattern in Lead aV_L, on the other hand, resembled that of V_4 and, along with the findings in the first four precordial leads, suggested infarction of the subendocardial layer of the basal portion of the anterolateral wall. The Q wave of aV_L was obliteread in Lead I because of the simultaneous greater negativity of the right arm. Death occurred before additional high precordial leads could be taken.

Pathologic Findings.—The heart weighed 341 grams and exhibited a calcareous aortic stenosis. By means of multiple microscopic blocks encircling the ventricle, an acute subendocardial infarct was found localized to the areas demarcated by the solid line in Fig. 7. This infarct involved the lateral wall at the base and extended diagonally forward into the anterior wall near the apex, but spared the septum and right ventricle. It apparently had occurred as a terminal event secondary to the peripheral circulator collapse consequent upon cerebral hemorrhage, which was the primary cause of death. The involvement of the anterior wall near the apex was probably responsible for the pattern in V_4, and the high lateral part of the infarct may have accounted for the findings in Lead aV_L. In view of the counterclockwise cardiac rotation and displacement of the transitional zone to the right, the infarction of the subendocardial layer of the anterolateral wall in the basal segment may have been responsible for the QR pattern in Leads V_1 and V_2. Since the electrocardiogram was obtained shortly before death, the bizarre findings may have reflected terminal functional changes independent of the demonstrated anatomical lesions.

Fig. 7.—Roentgenogram of the injected heart in Case 143.

CASE 144.—A 72-year-old man was admitted to the hospital in coma and died without regaining consciousness. No history was obtainable. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the first hospital day is reproduced in Fig. 5,*C*. In Leads V_6, V_7, and V_8 there was an exceptionally tall initial R wave, slightly delayed onset of intrinsicoid deflection, depression of the RS-T junction, and inversion of the T wave indicative of left ventricular hypertrophy. The QS complex in Lead V_1 and the minute R and deep S waves in V_2 were compatible with left ventricular hypertrophy. A triphasic QRS complex was recorded in the next three precordial leads. In Lead V_3 this was characterized by a Q wave 7.0 mm. in depth and 60 per cent of the succeeding R wave; in V_4 there was a Q wave 5.0 mm. in depth and 35 per cent of the subsequent upright deflection; whereas in V_5 there was a relatively small Q wave, which was only 7 per cent of the extremely tall R wave. The findings in Lead V_5, like those in V_6, were compatible with left ventricular hypertrophy. On the other hand, the findings in V_3 and V_4 were indicative of infarction and were attributed to a lesion involving the subendocardial portion of the anteroseptal wall of the left ventricle. Because of the slightly elevated, dome-shaped RS-T segment and sharply inverted T wave in these leads the infarct was considered to be of recent origin. For further localizing evidence, additional leads were obtained from points at the intersections of a horizontal line bisecting the junction of the third intercostal space and sternum with vertical lines through precordial Positions 3 through 6. A much deeper Q wave and smaller R wave were recorded in the high leads above Positions 3 and 4. This was interpreted as evidence that the major portion of the infarct was located high in the anteroseptal wall of the left ventricle. In the high anterior axillary lead, there was a 6.0 mm. Q wave which was about 15 per cent of the amplitude of the tall R wave. This was compatible with, but not diagnostic of, a thin subendocardial infarct, occupying but a small fraction of the greatly hypertrophied lateral wall. In both the high midaxillary lead and in aV_L there was a relatively small Q wave 2.0 to 4.0 mm. in depth followed by an exceptionally tall R wave, delayed intrinsicoid deflection, depressed RS-T junction, and inverted T wave, which were more in keeping with uncomplicated left ventricular hypertrophy than with infarction.

The findings in Lead aV_L coupled with those in aV_F indicated that the heart was in horizontal position. The tall R wave in aV_R was probably due to transmission of the potential variations of the posterobasal aspect of the left ventricle to the right arm.

Pathologic Findings.—Death was due to a cerebral hemorrhage which had ruptured into the fourth ventricle. The heart weighed 472 grams and showed considerable concentric left ventricular hypertrophy. By means of multiple microscopic blocks, a small organizing infarct was found localized to the subendocardial portion of the lateral wall of the left ventricle at the base, as outlined in Fig. 8. There was no evidence of infarction of the anteroseptal wall of the left ventricle. In view of the horizontal position revealed by Leads aV_L and aV_F and the displacement of the transitional zone to the right between precordial Positions 2 and 3, it is probable that sufficient counterclockwise rotation was present to bring the basal portion of the lateral wall of the left ventricle into a position which facilitated transmission of its potential variations to points on the precordium. In this manner the electrocardiographic patterns of infarction found in leads taken at the parasternal and midclavicular lines might be correlated with the pathologic demonstration of an infarct limited to the lateral aspect of the basal portion of the left ventricle.

Fig. 8.—Roentgenogram of the injected heart in Case 144, outlining the position of a subendocardial lateral infarct.

CASE 145.—A 54-year-old man gave a two-year history of transient retrosternal constriction and dyspnea, precipitated by exercise and promptly relieved by rest, but recalled no attacks of prolonged pain. He was admitted to the hospital in congestive heart failure with auricular tachycardia and gradually became compensated after the spontaneous return of sinus rhythm. On the twenty-eighth day auricular tachycardia recurred, resulting in sudden left ventricular failure and death.

Electrocardiographic Findings.—An electrocardiogram obtained before the administration of digitalis is reproduced in Fig. 5,*D*. The first four precordial leads showed an RS complex

and the last two showed a minute insignificant Q wave preceding a normal upright deflection. The R wave increased from 2.0 mm. in Lead V_1 to 8.0 mm. in V_2, remained constant in V_3, decreased to 4.0 mm. in V_4, and progressively increased in V_5 and V_6. The notched, equiphasic RS deflection in Lead V_4 suggested that the electrode lay over the septum and that the localized reduction in the R wave might have been a transitional effect. The RS-T segments and T waves of V_5 and V_6 were somewhat suggestive of an ischemic zone beyond the boundary of an infarct, but were compatible with uncomplicated left ventricular hypertrophy. The equiphasic QR deflection and inverted T wave in Lead aV_L were more distinctive than the findings in the precordial leads, but could not be properly interpreted until the portion of the heart which had the predominant effect on the potential variations of the left arm was determined. The findings in Lead aV_L were not transmitted from the posterobasal wall of the left ventricle because of the prominent R wave in Lead aV_F, which indicated that the potential variations of the posterior wall

Fig. 9.—Roentgenogram of the injected heart in Case 145.

of the left ventricle were directed downward. The findings in aV_L were probably not due to cavity potentials transmitted through the mitral orifice to the left arm because the cardiac position which facilitates such a pathway leads to the registration of an inverted P wave in Lead aV_L. It was therefore concluded that the heart was in intermediate position and that the potential variations of the epicardial surface of the lateral wall of the left ventricle had the predominant effect upon the QRS-T pattern in Lead aV_L. The QR complex in Lead aV_L was considered strongly suggestive of lateral infarction, but could not be regarded as pathognomonic because of the low voltage of the QRS complex and the Q-wave duration below 0.03 second. The findings in aV_L were carried over into Lead I, but the Q wave was reduced in depth in Lead I because of the concurrent initial negativity of the right arm. Four other electrocardiograms were taken

during the hospital course and showed no significant changes in the QRS complexes of either the precordial or limb leads and no changes in the T waves other than those attributable to digitalis. For this reason, the lesion was considered to be old and healed. For further localizing evidence, additional leads were obtained from points at the intersections of a horizontal line at the level of the junction of the third intercostal space and sternum with vertical lines through precordial Positions 4, 5, and 6. The tracing taken at the level of the third intercostal space in the mid-clavicular line closely resembled Lead V_4, and that taken high in the midaxillary line was almost identical with Lead V_6. However, the record from the anterior axillary line at the level of the third intercostal space was characterized by an abnormal QR complex and dome-shaped RS-T segment. This finding, when compared with the customary Lead V_5 and with other records taken at the same horizontal level, was diagnostic of a localized high lateral infarction.

Pathologic Findings.—The heart weighed 749 grams because of left ventricular hypertrophy. A patchy healed infarct which involved the subendocardial one-half of the lateral wall, as outlined in Fig. 9, was found grossly and confirmed microscopically. The extension into the posterolateral wall of the apex was not evident in Lead aV_F, but might have constituted an indirect factor in the relatively high R waves in Leads V_2 and V_3. The infarction of the basilar portion of the lateral wall adequately accounted for the QR pattern in aV_L and in the lead high in the anterior axillary line, whereas the absence of infarction of the anterolateral aspect of the apex could explain the lack of a diagnostic pattern in Leads V_4, V_5, and V_6. This case illustrates well the value of supplementary high precordial leads in the diagnosis of infarcts situated high in the lateral wall of the left ventricle.

CASE 146.—A 72-year-old man had had classical angina pectoris for two years. On June 1, 1945, he was seized with a much more severe attack of retrosternal constriction followed by syncope. He was brought to the hospital in shock one hour later and remained in profound circulatory collapse until his death thirty-nine hours after admission.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 10 were obtained on June 1, two hours after the onset of the pain and before the administration of cardiac glycosides, and on June 2, twenty-two and one-half hours later, after the administration of 1.6 mg. of Cedilanid. In the record of June 1, there was a marked sinus bradycardia (36 per minute) with occasional escaped nodal beats. The initial phase of the QRS complex was upright and normal in contour in all precordial leads. The striking feature of the first five precordial leads was the marked depression of the RS-T junction, the exceptionally broad U-shaped T wave, which caused moderate prolongation of the Q-T interval. The administration of quinidine and allied drugs could be excluded positively. Two possible causes for the RS-T depression remained for serious consideration: (1) a reciprocal manifestation of a recent posterolateral infarct; and (2) a direct result of acute ischemia or early infarction of the subendocardial portion of the anterolateral wall of the left ventricle and the adjoining left side of the septum. The slight elevation of the RS-T junction in Leads V_6 and aV_F raised the question of recent posterolateral infarction. The absence of a Q wave from these leads and the contour of the RS-T segment and T wave were against posterolateral infarction, but did not exclude it, because of the short interval between the onset of symptoms and the recording of the electrocardiogram. Nevertheless, a diagnosis of acute ischemia or very early infarction of the subendocardial portion of the anterolateral wall of the left ventricle and left side of the septum was favored in the ante-mortem interpretation because the downward displacement of the RS-T segment in the first five precordial leads greatly exceeded the upward displacement in V_6 and aV_F. Lead aV_L showed an M-shaped QRS complex of very low voltage and an inverted T wave, which were probably transmitted from the transitional zone as a result of semivertical position of the heart. In the next tracing there was no significant change in the QRS pattern in the standard leads or in aV_R, aV_L, V_1, and V_2. The initial phase of the QRS complex was still upright in the four remaining precordial leads, but was reduced to approximately one-third of its former voltage. The marked decrease in the amplitude of the R wave in these leads was suggestive of patchy infarction of the anterolateral wall of the left ventricle. Close scrutiny of Lead aV_F disclosed the appearance of a minute Q wave 0.5 mm. in depth without significant change in the upright deflection. Although this Q wave was too small to be of diagnostic significance, the parallelism of the T-wave evolution to that of Lead V_6 suggested that the lesion

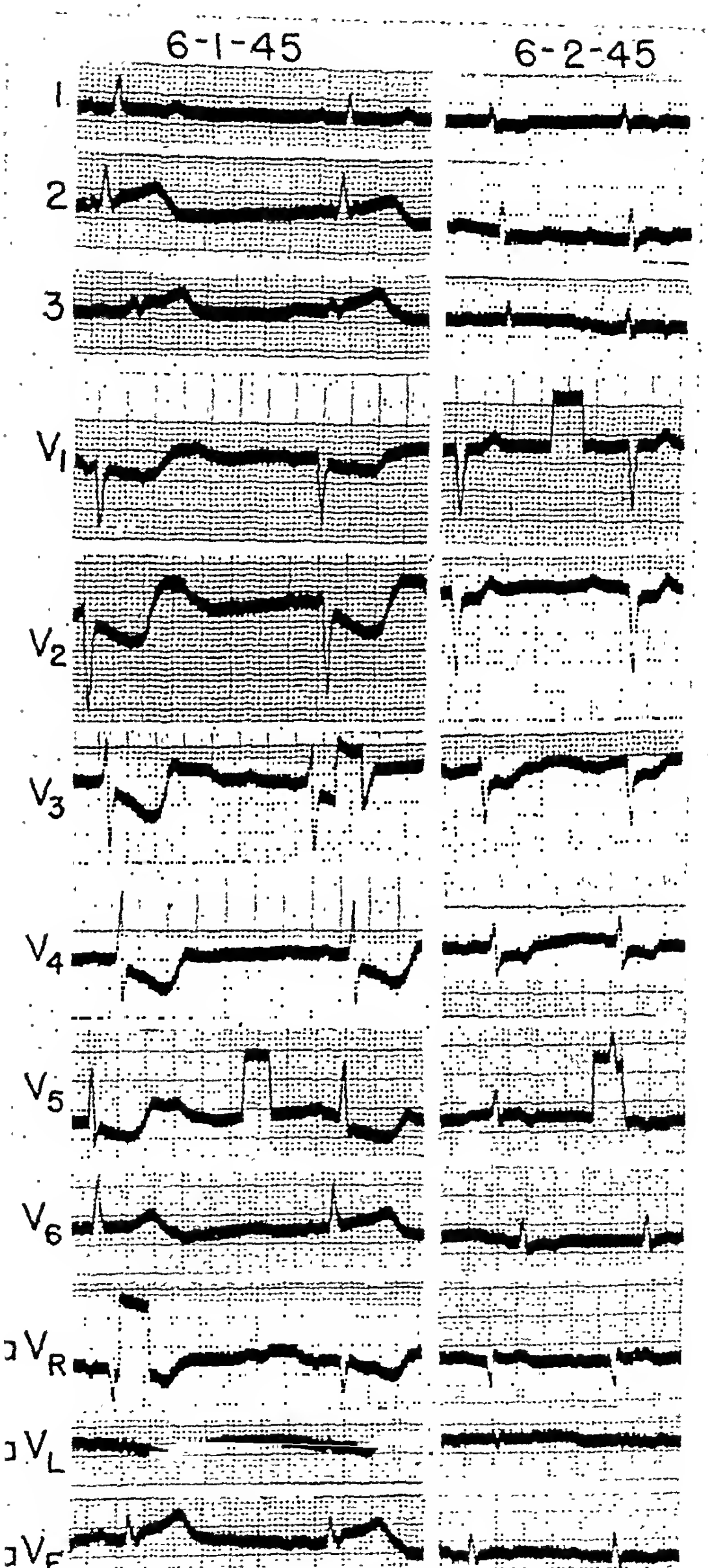

Fig. 10. Serial electrocardiograms in Case 146.

responsible for the changes in V_6 was so placed as to influence the potential variations of the left leg as well. However, the changes in the RS-T segment and T wave were difficult to evaluate because of the administration of Cedilanid during the interim between the two tracings. The marked shortening in the Q-T interval to normal could be ascribed to the combined effects of the acceleration in rate and the Cedilanid. On the other hand, the domelike contour of the RS-T segment in Leads V_5, V_6, and aV_F is an unusual manifestation of cardiac glycosides, but may be produced by toxic doses. The combination of the reduction in voltage in the R wave and the appearance of a domelike RS-T segment and inversion of the terminal portion of the T wave of V_5 and V_6 was more likely a manifestation of a patchy infarct with associated epicarditis involving the lateral wall of the left ventricle and extending sufficiently into the posterior aspect to account for the pattern in Lead aV_F. Although a considerable change had occurred in the contour of the RS-T segment and T wave in Leads V_1 through V_4, the magnitude of the depression of the RS-T junction in V_2 through V_4 was almost as great as in the first tracing. The question still arose as to whether this depression was a reciprocal manifestation of a recent posterolateral infarction or a direct result of acute ischemia or early patchy infarction of the subendocardial portion of the anteroseptal wall.

Fig. 11.—Roentgenogram of the injected heart in Case 146 with lateral infarct outlined in black and the anteroseptal ischemia demarcated by its lack of injection.

Pathologic Findings.—The heart weighed 560 grams and showed moderate left ventricular hypertrophy. The striking feature of the roentgenogram (Fig. 11) was the lack of injection of the entire anterior wall of the left ventricle and septum, which was due to an occlusion of the anterior descending coronary artery near its origin. Nevertheless, several microscopic sections through this avascular area showed no evidence of infarction. On the other hand, definite microscopic signs of recent infarction were found in the lateral wall of the left ventricle, as demarcated by the solid lines of Fig. 11. This lateral infarct was transmural at the base and subendocardial at the apex and was probably responsible for the abnormal reduction in the amplitude of the R wave in

Leads V_5 and V_6 and for the T-wave changes in these leads. Since the heart was in semivertical position, sufficient clockwise rotation may have been present to permit transmission of the potential variations of the infarcted area to the left leg, thereby causing the T-wave evolution in aV_F. In view of the occlusion of the anterior descending coronary artery, it is probable that there was sufficient ischemia of the subendocardial portion of the anterior wall of the left ventricle and septum to have caused the downward displacement of the RS-T segment in the first four precordial leads. This seems a more logical explanation of the marked displacement than a reciprocal manifestation of the lateral infarct.

CASE 147.—A 65-year-old man gave a history of intermittent attacks of retrosternal pain, radiating down both arms, accompanied by dyspnea, precipitated by exertion, and relieved by rest. However, he remained at work until one week before hospital admission, when he was suddenly seized with a much more severe epigastric pain accompanied by marked prostration. He entered the hospital because of persistence of the pain and increasing dyspnea. Death occurred fifty-four hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained thirty-five hours after admission is reproduced in Fig. 12,*A*. In Lead aV_L there was a QR complex, consisting of a Q wave 3.0 mm. deep, an R wave 4.0 mm. tall, an elevated RS-T segment, and a sharply inverted T wave. Although these findings strongly suggested lateral infarction, it was necessary to consider the possibility that they might have been due to transmission of the potential variations of the normal left atrium to the left arm. The P wave in aV_L was isoelectric and thus of no aid in the differential diagnosis. Considerable indirect help was obtained from the QRS pattern in Lead aV_R. If the QR complex in aV_L had been due to vertical position of the heart, a comparable QR or a QS wave should have been registered in Lead aV_R. The presence of a prominent initial R wave in Lead aV_R was against vertical position, but was compatible with the presence of lateral infarction. The small triphasic QRS complex of Lead aV_F was considered transitional and due to transmission of the potential variations of the posterior aspect of the interventricular septum to the left leg. An abnormal Q wave was registered in Lead I because of the initial positivity of the right arm as well as the negativity of the left arm. A small Q wave was found in Lead II because of the initial positivity of the right arm. Thus, the standard leads were in accord with the diagnosis of lateral infarction. Signs of the lateral infarct evident in Lead aV_L and in the standard leads were not found in V_5 and V_6. An RS deflection and an upright T wave were registered in Leads V_2 through V_6 and were of comparable contour, merely exhibiting a gradual increase in the ratio of the R wave to the S wave as the electrode was moved to the left. The findings in Leads V_2 through V_6 were considered transitional in origin as a result of parallelism between the long axis of the interventricular septum and the pathway of the electrode from Position 2 to Position 6. Thus, Leads V_2 through V_4 were dominated apparently by the potential variations of an area on the anterior surface just to the right of the interventricular septum, while V_5 and V_6 were probably dominated by potential variations of a point on the anterolateral surface just to the left of the interventricular septum and hence would not reveal evidence of lateral infarction. In Lead V_1 there was a QR complex, elevated RS-T junction, and inverted T wave much like the findings in aV_L. The pattern in Lead V_1 resembled that in the corresponding lead in Case 143 and was attributed to extension of the lateral infarct into the basal portion of the anteroseptal wall of the left ventricle. In the differential diagnosis the possibility of right ventricular hypertrophy was considered because of the prominent initial R wave in aV_R, the late upright deflection in V_1, and the prominent S wave in the remaining precordial leads.[15] Although right ventricular hypertrophy may be responsible for a small Q wave in precordial leads over the right ventricle, it should at the same time produce a much larger R wave than that present in Lead V_1 of this patient, along with depression, rather than elevation, of the RS-T junction. The pattern in Lead V_1 was thus considered to be much more consistent with infarction than with right ventricular hypertrophy. From the RST-T pattern in Leads aV_L and V_1, the infarct was considered of recent origin.

Pathologic Findings.—The heart weighed 562 grams and exhibited left ventricular hypertrophy. A recent infarct was found in the basal one-half of the lateral wall and was comparable in size and position to the lesion of the two basilar segments in Case 143 (Fig. 7), except that it

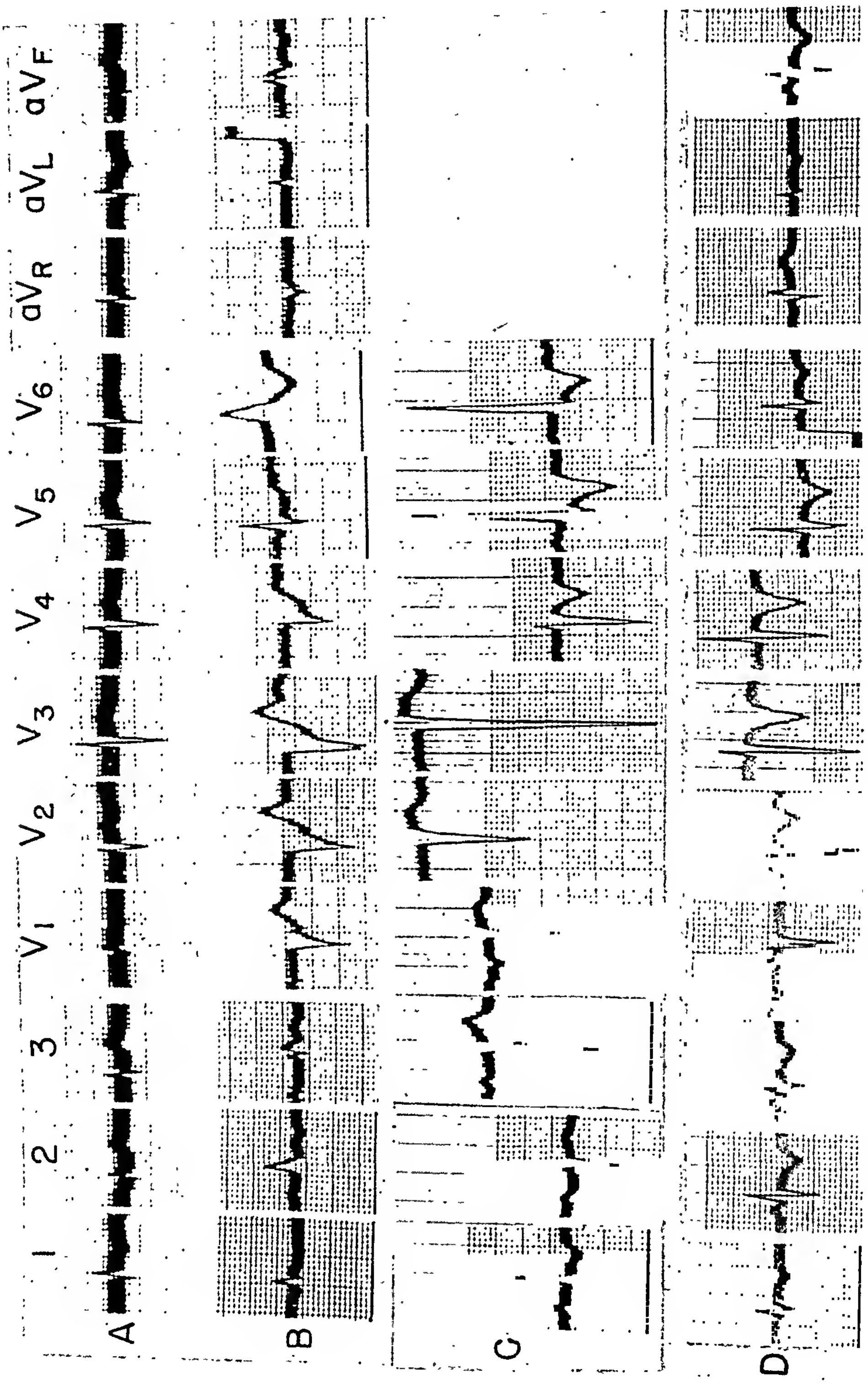

Fig. 12.—Electrocardiograms in lateral infarction. *A*, Case 147; *B*, Case 148; *C*, Case 149; *D*, Case 150.

extended slightly farther into the anterior wall. The infarct tapered toward a blunted point in the mid-portion of the lateral wall. No evidence was found of infarction of the septum or right ventricle. There was good correlation between the infarct of the basal portion of the lateral wall and the QR pattern in Lead aV_L. Since no other explanation was found for the abnormal QR pattern in V_1, it may be have been a manifestation of the continuation of the infarct into the basilar portion of the anterolateral wall.

CASE 148.—A 73-year-old man gave a history of intermittent attacks of retrosternal pain and dyspnea, which were brief in duration, until the evening prior to hospital admission. At that time he was seized with a much more severe attack which lasted all night. He was admitted in shock and remained in severe circulatory collapse until his death four days later.

Electrocardiographic Findings.—An electrocardiogram, obtained two hours after admission and following the administration of 1.6 mg. of Cedilanid, is reproduced in Fig. 12,*B*. There was an underlying sinus rhythm with P-R interval of 0.30 to 0.32 second, complicated by episodes of escaped ventricular rhythm with interference dissociation. The abnormalities in rhythm may have been a result of the Cedilanid. The striking feature of the precordial leads was the very marked RS-T depression in Leads V_2 through V_4 and moderate depression in V_1 and V_5. It was believed that this was independent of Cedilanid action because the Q-T interval was well above the limits of normal and because digitalis glycosides tend to produce elevation of the RS-T segment in leads where the major portion of the QRS complex is downward and depression in leads where the major portion of the QRS is upright. Two possibilities remained for consideration: (1) acute infarction or ischemia of the subendocardial portion of the anteroseptal wall of the left ventricle, and (2) a reciprocal pattern secondary to recent posterolateral infarction. Because of the presence of a definite initial R wave in Lead V_{3R} and a slurred or notched QS complex in V_1 through V_4, an ante-mortem diagnosis was made of a recent infarct involving chiefly the subendocardial portion of the anteroseptal wall of the left ventricle. In addition, the presence of a posterolateral infarct was suspected from the findings in Leads V_6, aV_L, and aV_F. In cycles of supraventricular origin in Lead aV_F, there was a coarsely notched M-shaped QRS complex measuring 0.15 second in duration, a longer duration than was present in any other unipolar lead. This was interpreted as evidence of a conduction defect in the posterior wall of the left ventricle of a type which could be due to fibrosis from remote infarction. The RS-T segment in Leads aV_F, aV_L, and V_6 was iso-electric to slightly elevated and showed a distinct upward bowing, and ended in a shallowly inverted T wave. The contour of the RS-T segment and T wave in these leads was atypical of Cedilanid and suggestive of a lesion of the subepicardial portion of the lateral wall, but the findings were considered too meager to justify a definite diagnosis. The electrocardiogram was therefore interpreted as indicating a recent infarct of the subendocardial portion of the anteroseptal wall of the left ventricle which extended into the left side of the septum and was probably accompanied by an old lesion in the posterior wall, perhaps the result of infarction. Unfortunately, no further tracings were obtained.

Pathologic Findings.—The heart weighed 442 grams and revealed a large recent infarct occupying the entire lateral wall. The involvement of the basilar one-half of the lateral wall was comparable to that of the recent infarct in Case 153 (Fig. 17). The recent lesion continued into the basilar one-half of the posterolateral wall, where it was confluent with an old, patchy fibrosis, resulting from an old, healed posterobasal infarct. It its apical portion, the recent infarct extended diagonally forward to involve the subendocardial one-half of the anterolateral wall. The unusual RST-T pattern in Leads V_6 and aV_L was probably a manifestation of the recent lateral infarct. The lack of a diagnostic QRS pattern in V_6 and aV_L might have been due to patchy distribution of the lesion at the time the electrocardiogram was taken, with subsequent confluence as a result of a persistent shocklike state during the next four days. If the RS-T depression in the first four precordial leads had been merely a reciprocal manifestation of the recent posterolateral infarct, a definite, if not exaggerated, initial R wave would have been expected in these leads. No evidence of anteroseptal infarct was found at autopsy to account for the abnormal QS complexes in these leads. Since the infarct extended into the subendocardial portion of the lateral one-half of the anterior wall, a moderate counterclockwise rotation might have permitted transmission of the potentials of the infarcted region to the anterior chest wall, thereby

making the pattern in V_2 through V_4 a direct manifestation of the infarct. The depression of the RS-T segment in these leads may have been augmented as a result of the reciprocal effects of the recent posterolateral infarct. The fibrosis of the posterior wall could have explained the broad M-shaped QRS complex in Lead aV_F and may have been responsible for the broadening of the S wave in the first four precordial leads.

CASE 149.—A 64-year-old man had had no cardiovascular symptoms until two weeks before hospital admission, when he was suddenly stricken with severe dyspnea while climbing one flight of stairs. Thoracic pain was denied. Progressive cardiac failure occurred during the next fortnight, leading to admission. While in the hospital, he had several attacks of auricular tachycardia with prolonged P-R interval. The last attack caused recurrence of heart failure and death on the thirty-seventh hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the twenty-second day, while the patient was taking maintenance doses of digitalis, is reproduced in Fig. 12,*C*. The QRS pattern in the precordial and limb leads was essentially the same as that in five other tracings taken at intervals during his five-week hospital stay. The tall R wave and slightly delayed intrinsicoid deflection in Leads V_5 and V_6 were indicative of left ventricular hypertrophy. Serial tracings revealed gradually increasing RS-T depression in Leads V_5 and V_6 together with progressive deepening of the consistently inverted T waves. It was believed that left ventricular hypertrophy was basically responsible for the depression of the RS-T segment and negativity of the T wave, and the question arose as to whether the progression was due entirely to digitalis or in part to a lesion of the subendocardial portion of the lateral wall. Because of the patient's condition, digitalis could not be withheld for a period long enough to settle this question. Lead aV_L closely resembled V_6, whereas aV_F showed small R and deep S waves due to horizontal position. The QS complex consistently recorded in V_1, V_2, and V_3 may have been due to anteroseptal infarction or may have constituted a variant occasionally found in uncomplicated left ventricular hypertrophy. Although recent anteroseptal infarct seemed excluded by the absence of significant serial changes in the T wave, a positive differentiation between old, healed anteroseptal infarction and uncomplicated left ventricular hypertrophy was not made. Thus, the only definite diagnosis made from the electrocardiogram was left ventricular hypertrophy with digitalis effect, but the possibilities of old, healed anteroseptal infarct and a more recent lesion confined to the subendocardial portion of the lateral wall were seriously considered.

Pathologic Findings.—The heart weighed 694 grams as a result of left ventricular hypertrophy secondary to rheumatic aortic stenosis. A relatively small organizing infarct was found, confined to the subendocardial one-fourth of the lateral wall in the middle one-third of the left ventricle. The position and size of this infarct corresponded closely with that in the third and fourth segments in Case 144 (Fig. 8). It is possible that this infarct was in part responsible for the progressive depression of the RS-T junction and deepening of the inverted T wave in Leads V_5 and V_6. The absence of Q waves from these leads was probably due to the relatively small size of the infarct in comparison with the bulk of the surrounding hypertrophied, but uninfarcted, anterolateral wall. Since there was no evidence of anteroseptal infarction, the QS complex in Leads V_1, V_2, and V_3 was apparently a variant sometimes encountered in left ventricular hypertrophy.

CASE 150.—A 65-year-old man gave a history of shortness of breath on exertion for five years, but continued to work as machinist until a few days before hospital admission, when he was completely incapacitated because of an abrupt increase in dyspnea. Thoracic pain was denied. He was admitted in congestive heart failure and died four days later.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day, after the administration of 1.6 mg. of Cedilanid, is reproduced in Fig. 12,*D*. In all precordial leads, in aV_L, and in aV_F the initial deflection was upright and the QRS complex was considered to be within the limits of normal. The striking feature was the deeply inverted T wave with isoelectric RS-T junction in Leads V_2 through V_6, in Lead aV_F, and in the standard leads. Because of the contour of the RS-T segment and T wave and the relatively long Q-T interval, the abnormalities in the RS-T complex were not due primarily to Cedilanid. The widespread distribution of the inverted T wave, as well as its contour and depth, was typical of a diffuse lesion of the sub-

epicardial layer, maximal in the anterolateral wall of the left ventricle. The ante-mortem electrocardiographic diagnosis rested between pericarditis and a subepicardial infarct.

Pathologic Findings.—The heart weighed 400 grams and showed definite evidence of *right* ventricular dilatation and hypertrophy secondary to obstructive emphysema. There was *no* gross evidence of pericarditis. Multiple microscopic blocks showed an extensive subepicardial lesion which involved the entire lateral wall and overlapped onto the anterior and posterior walls of the left ventricle, corresponding closely in position and surface area to the entire infarct of the outer wall of the left ventricle in Case 153 (Fig. 17). In all microscopic blocks the lesion was limited to the subepicardial layer and was considered to be the result of infarction rather than inflammation. The deep inversion of the T waves and the normal QRS pattern in Leads V_2 through V_6 and aV_F corresponded satisfactorily with the subepicardial infarct found at autopsy. The right ventricular hypertrophy was missed electrocardiographically because of the absence of diagnostic changes in the QRS complex.* The low upright T wave in right ventricular Lead V_1 indicated that the T-wave inversion of the other leads was independent of right ventricular hypertrophy.

CASE 151.—A 70-year-old man was admitted to Grace Hospital in cardiac failure on March 19, 1946, with a history of shortness of breath for one week and tightness in the chest and pain in the left shoulder and arm for one day. He was readmitted on May 27, 1946, because of vise-like precordial pain of two days' duration and had a clinical course compatible with myocardial infarction. Digitalis was instituted and maintained for the rest of his life. Ever since discharge, he was partially incapacitated because of exertional and paroxysmal nocturnal dyspnea. He was admitted to Receiving Hospital in shock on Feb. 26, 1947, eighteen hours after the onset of a third attack of prolonged retrosternal pain. Death occurred one week later.

Electrocardiographic Findings.—An electrocardiogram† obtained on March 19, 1946, before the administration of digitalis, and two subsequent tracings, while the patient was on maintenance doses, are reproduced in Fig. 13. In the first five precordial leads on March 19, 1946, an initial upright deflection was registered, whereas in V_6 there was a 2.5 mm. Q wave which was 0.03 second in duration and 33 per cent of the amplitude of the succeeding R wave. This Q wave and the slurred ascending limb of the R wave, which was 0.04 second in duration, were considered abnormal and referable to infarction of the subendocardial portion of the lateral wall. The standard leads showed marked left axis deviation with pronounced slurring or notching, but were not diagnostic of infarction. In Lead V_6 obtained on June 4, 1946, the Q wave was smaller, but the QR complex was still abnormal, though no longer diagnostic of lateral infarction. The T wave in this lead displayed signs of digitalis effect. The most striking change took place in Leads V_2 through V_4 and consisted in sharp inversion of the T wave, without significant difference in the QRS complex. The reversal in direction of the T wave in these leads was not due solely to digitalis, since the effect of this drug on a pattern like that recorded in Leads V_2 through V_4 on March 19 is to cause further elevation of the RS-T junction, straightening of the RS-T segment, and increase in the amplitude of the upright T wave, along with reduction in the QT interval. The underlying cause for the reversal in these T waves may have been an intramural anteroseptal infarction, an anteroseptal ischemic zone consequent upon extension of the lateral infarct high in the basal portion of anterolateral wall, or acute right ventricular dilatation. The latter was unlikely because of the fact that the T-wave inversion was not nearly as deep in V_1 as in leads farther to the left. Leads V_1 to V_3 recorded on March 3, 1947, showed RS complexes comparable to those in the same leads of previous tracings. The formerly inverted T waves in these leads had become upright. On the other hand, the slurred QS complex recorded in Lead V_4 and the abnormal QR complex in V_5 differed significantly from the findings in previous records and indicated that infarction of the anterior and anterolateral wall of the left apex had occurred some time since the tracing of June 4, 1946. The T-wave pattern in these leads was not characteristic of recent

*This case was previously reported as Case 38 of a paper on right ventricular hypertrophy.[15]

†The first two electrocardiograms and the information relevant to his course at Grace Hospital were furnished through the courtesy of Dr. L. T. Colvin. The record of Lead V_3 on March 19, 1946, was the only cycle available on the chart and showed a much broader QRS complex than in other leads, suggesting that it was a ventricular premature beat.

infarction and might have been the result of digitalis. No significant change had occurred in the QRS complex of Lead V_6. To investigate further the possibility of a high lateral infarct, tracings were obtained above precordial Positions 4, 5, and 6 on a horizontal line at the level of the junction of the third intercostal space and sternum. The records taken above Positions 4 and 5 resembled closely the QR complex registered at the customary fifth precordial position. The tracing high in the mid-axillary line above Position 6 was characterized by a Q wave of 2.0 mm., an R wave of 5.0 mm., an isoelectric RS-T junction, convex upward RS-T segment, and inverted T wave. The QR pattern in this lead was thus more abnormal than in either the customary Lead V_6 or Lead aV_L, and suggested that the infarct extended high in the subendocardial portion of the lateral wall.

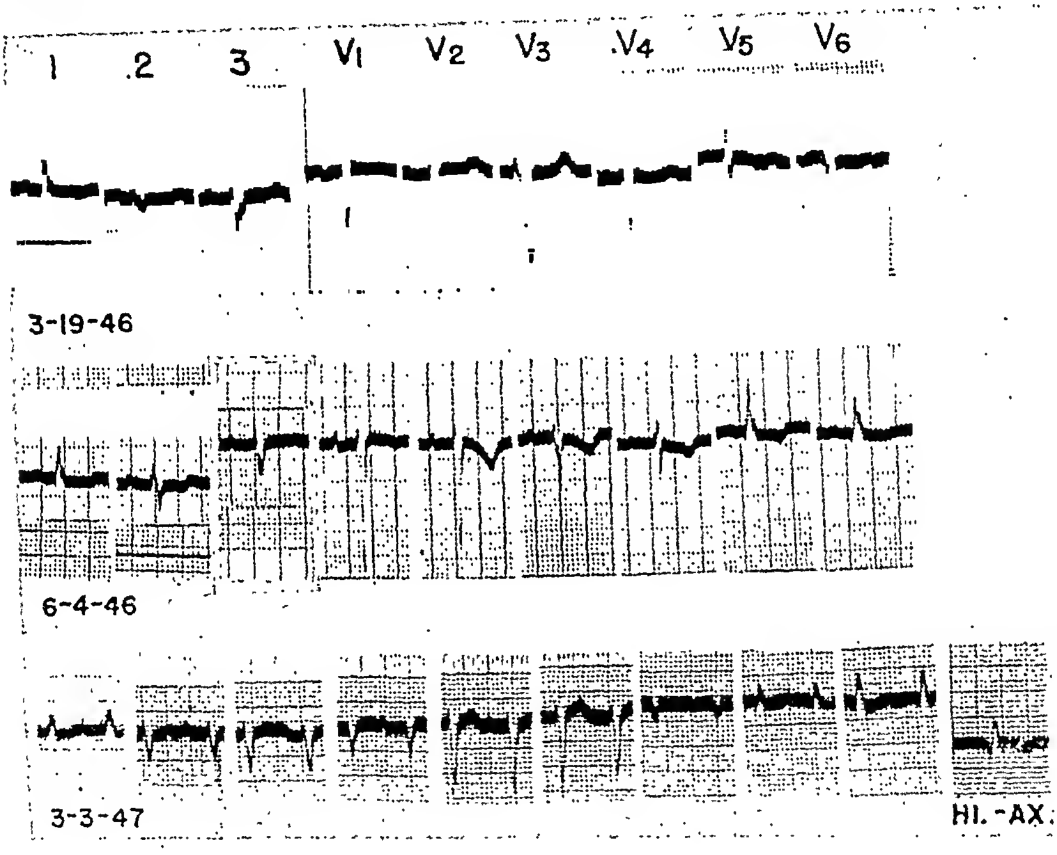

Fig. 13.—Serial electrocardiograms in Case 151.

Pathologic Findings.—The heart weighed 562 grams and exhibited an old, healed infarct of the entire lateral wall and a recent infarct of the subendocardial portion of the anterior wall and left side of the septum. The old infarct occupied the posterolateral aspect of the apex and extended diagonally forward and upward so as to involve the anterolateral wall at the base where the wall was thin and outpouched to form a ventricular aneurysm, as represented by the broken lines of Fig. 14. The position of the recent infarct was outlined by solid lines. Microscopic sections showed that the old infarct involved almost the entire thickness of the wall, whereas the recent infarct was limited to the subendocardial one-half. The old infarct of the lateral wall was probably responsible for the abnormal QR pattern in Lead V_6 recorded on March 19, 1946. An extension into the anterolateral portion of the fifth and sixth segments on May 25, 1946, seemed the best explanation for the reversal of the T waves in Leads V_2, V_3, and V_4 recorded on June 4, 1946. According to this hypothesis, the findings in these leads were representative of an outlying ischemic zone. The findings in Lead V_6 and the high axillary lead of the final tracing

were probably a residue of the old infarct, whereas those in V_4 and V_5 were presumably the result of the more recent anteroapical infarct. Leads V_1, V_2, and V_3 gave no definite indication of the involvement of the left side of the septum. The extension of the old infarct into the posterolateral wall of the apex was not revealed by the standard leads on any occasion or by Lead aV_F on the final admission.

Fig. 14.—Roentgenogram of the injected heart in Case 151, showing recent anteroseptal infarct in solid outline and old, healed lateral infarct in broken lines.

Case 152.—A 59-year-old man gave a typical history of angina pectoris, beginning in October, 1942, and myocardial infarction, occurring in November, 1943. His second attack of prolonged retrosternal pain began on March 10, 1944, and led to hospitalization in congestive failure the next day. He was given 1.6 mg. of Cedilanid soon after admission, but received no further cardiac glycosides until March 26, when digitalization was carried out and maintained for the rest of his life. His third attack of prolonged retrosternal pain began on May 17, 1944, and led to readmission in shock the following day. Death occurred twenty-five hours after admission.

Electrocardiographic Findings.—Electrocardiograms reproduced in Fig. 15 were obtained on March 13, three days after the onset of the second attack of prolonged retrosternal pain, on April 22, while the patient was under observation in the out-patient department, and on May 19, two days after the onset of his third attack. The QRS complex was 0.12 second in duration and was slurred or notched abnormally in several leads. The conduction defect was located in

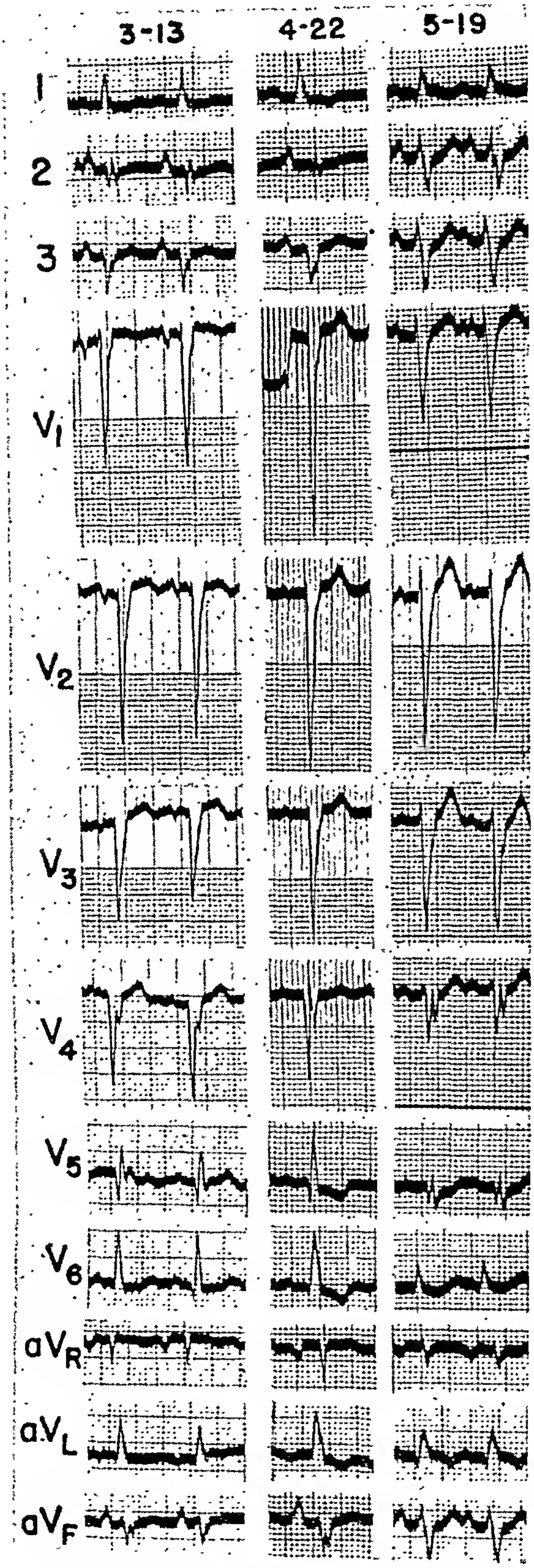

Fig. 15.—Serial electrocardiograms in Case 152.

the left ventricle, because of the delayed onset of the intrinsicoid deflection in Lead V_6, and was attributed to anterolateral infarction, because of the abnormal QR pattern in V_5. In the first four precordial leads, the electrode was judged to be to the right of the interventricular septum, because of the minute R wave and the deep, broad, slurred S wave. The most significant features of the pattern in the first three precordial leads were an initial Q wave 0.5 to 1.0 mm. in depth and the diminishing height of the R wave as the electrode was moved toward the left. These findings were interpreted as evidence of continuation of the anterolateral infarct into the left side of the interventricular septum. From the RST-T contour in the tracing of March 13, it was thought that the infarct was old and healed. However, two tracings taken during the next ten days revealed no significant change in the QRS contour, but showed progressive inversion of the T waves in Leads V_5, V_6, aV_L, and Lead I, to reach a pattern comparable to that in the tracing of April 22. Since no cardiac glycosides were given during this period, drug effects were excluded. The T-wave evolution pointed to a recent anterolateral infarction, which may have been superimposed on an older lesion in the same area. The minute, slurred R wave and broad, notched S wave consistently recorded in Lead aV_F were presumably transmitted from the posteroinferior surface of the right ventricle as a result of horizontal position of the heart. To investigate the possibility of posterior infarction, esophageal leads were obtained on April 22. Records from the ventricular level showed a small Q wave which ranged from 8 to 33 per cent of the succeeding R wave. Although the Q/R ratio was not definitely abnormal, the fact that the Q wave was accompanied by coarse notching of the R wave was strongly suggestive of a patchy lesion in the posterior wall. In the final tracing, the most striking change occurred in Lead aV_L and secondarily in Lead I. It was characterized by the appearance of a slurred Q wave 0.03 second in duration, by a significant reduction in the amplitude of the R wave, and by upward displacement of a formerly depressed RS-T junction. These changes, along with the marked reduction in the amplitude of the R wave in Leads V_5 and V_6 and the reciprocal increase in the R and T waves of aV_F and the first three precordial leads, were diagnostic of acute reinfarction of the lateral wall of the left ventricle.

Pathologic Findings.—The heart weighed 614 grams and revealed a recent lateral infarct almost identical in size, shape, and position with the recent infarct in Case 142 (Fig. 6). In addition, an old, healed subendocardial anteroposterior infarct was found, involving the subendocardial one-half of the entire posterior wall, the apical one-third of the anterior and lateral walls, and the apical one-half of the left side of the septum. The abnormal pattern in Leads V_5 and V_6 of the early tracings could be correlated with the anterolateral portion of the old infarct, whereas the initial Q wave in V_1, V_2, and V_3 was apparently a manifestation of involvement of the left side of the septum. The absence of diagnostic signs of the posterior infarction in Lead aV_F was probably the result of horizontal position of the heart with reference of the potential variations of the posterior inferior surface of the right ventricle to the left leg. The Q and notched R waves recorded in esophageal leads at the ventricular level were probably a manifestation of the posterior infarction, but the Q/R ratio was lower than would have been expected from a lesion involving the subendocardial one-half of the wall. The recent lateral infarct was found chiefly in the subendocardial one-half, but extended in fingerlike fashion to the epicardium. The changes in Leads I, aV_L, V_5, and V_6 of the final tracing could be correlated with the terminal lateral infarct.

CASE 153.—A 65-year-old woman gave a history of myocardial infarction in 1935, from which she made an uneventful recovery, remaining symptom free until 1940. After three years of gradually increasing dyspnea, congestive failure occurred, necessitating hospitalization in October, 1943. Digitalization was carried out and continued for the rest of her life. Compensation was maintained until Jan. 6, 1944, when there was a sudden recurrence of dyspnea without associated chest pain, followed by progressive cardiac failure during the next two weeks. She was readmitted in extreme decompensation on Jan. 19, 1944, and died two weeks later.

Electrocardiographic Findings.—Electrocardiograms from the two hospital admissions are reproduced in Fig. 16. On Oct. 21, 1943, the QRS complex measured 0.12 second and was notched or slurred in a number of leads, thus establishing the presence of an intraventricular conduction defect. The time interval of 0.07 to 0.08 second from onset of the QRS complex to the beginning

of the intrinsicoid deflection in Leads V_5 and V_6 signified a delay in conduction of the impulse through the left ventricle. The Q waves preceding the later intrinsicoid deflections in these leads excluded uncomplicated left bundle branch block and were typical of a conduction defect in the anterolateral wall of the left ventricle. Left bundle branch block associated with complete destruction of the septum was considered in the differential diagnosis, but was ruled out by insufficient prolongation of the QRS complex. Although the Q/R ratio in Lead V_5 was only 15 per cent, the Q wave was abnormal because of the 0.03 second interval from onset to nadir, and

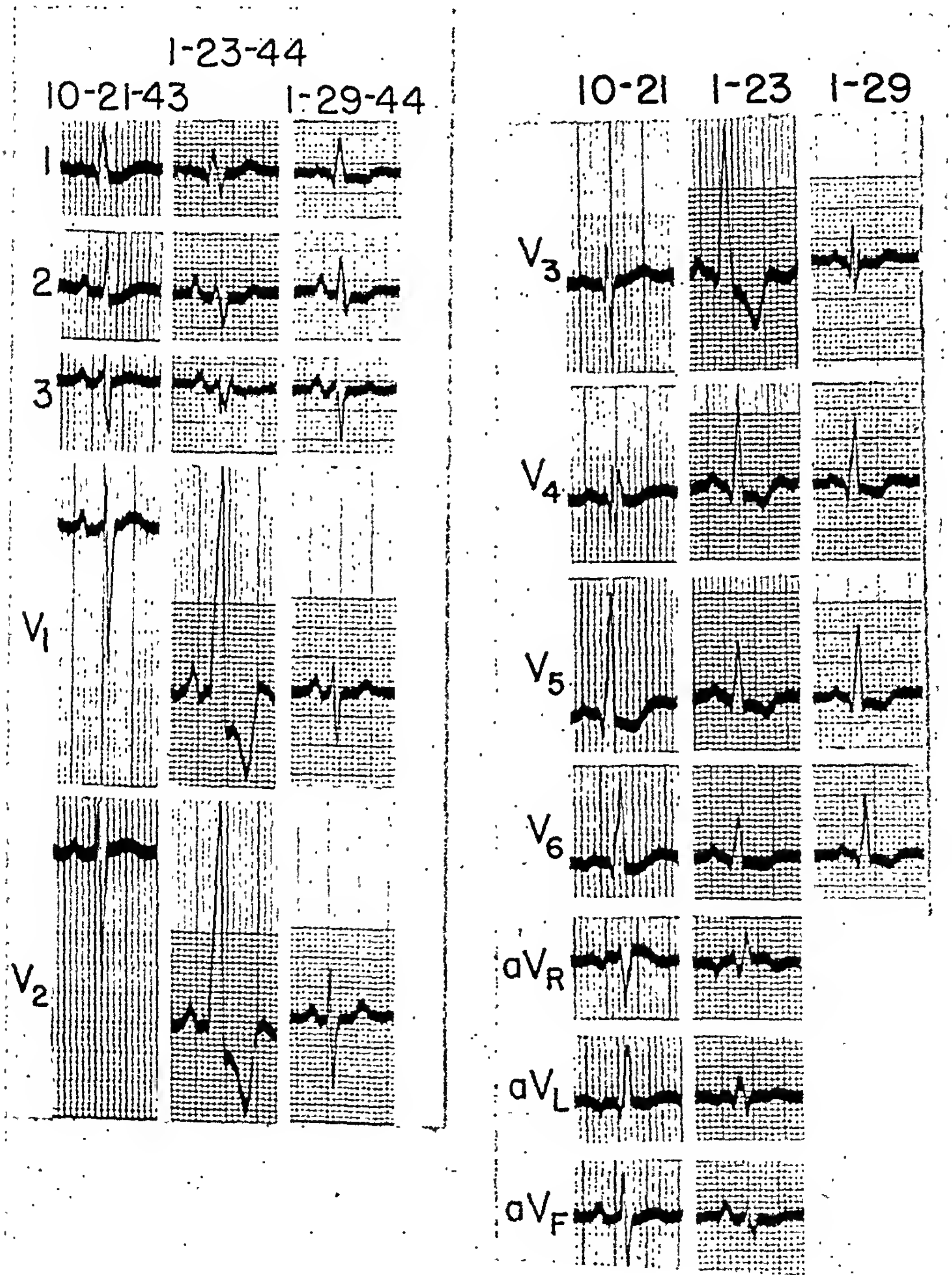

Fig. 16.—Serial electrocardiograms in Case 153.

the R wave was abnormal because of the coarse slurring and the 0.05 second interval between its onset and peak. A QR complex in Leads V_5 and V_6 characterized by a prolonged Q wave and an abnormally broad, slurred, or notched upstroke was regarded as a typical manifestation of anterolateral infarction, densely distributed in the subendocardial layer and patchy in the remainder of the wall. The association of a Q wave and notched R wave pointed more toward old than recent infarction. However, positive conclusions as to the age of the lesion on the first admission were not justifiable from the electrocardiographic findings alone, since the RS-T complex was distorted by digitalis action in the single record obtained. The presence of a Q wave and abnormal Q/R ratio in V_3 and V_4 and the fact that the upright deflection in these leads was smaller than the initial R wave of right ventricular Leads V_1 and V_2 constituted evidence that the infarct extended subendocardially into the apical portion of the anteroseptal aspect of the left ventricle. The inverted P wave in Lead aV_L suggested that the QR complex may have been transmitted from the posterobasal rather than the lateral wall of the left ventricle and thus left the

Fig. 17.—Roentgenogram of the injected heart in Case 153, showing position of recent high lateral infarct and old anterolateral posterior apical infarct.

interpretation of the findings in aV_L and Lead I in doubt. In the tracing of Jan. 23, 1944, the QRS interval had increased to 0.16 second and a striking change had occurred in the QRS-T pattern of Leads V_1 through V_3, characterized by the appearance of a very tall R wave, markedly depressed RS-T junction, and deeply inverted T wave. On the other hand, the QRS pattern in Leads V_5 and V_6 showed no significant change apart from a 50 per cent reduction in the voltage of the R wave. The upright initial deflection in V_1 and V_2, together with the delay of the intrinsicoid deflection in these leads to 0.08 second, indicated that the newly developed conduction defect was in the right side of the septum and consisted of right bundle branch block. Since the P-R interval on January 23 was 0.16 second, the possibility of an intermittent Wolff-Parkinson-White syndrome was excluded. The development of the right bundle branch block was manifested by the appearance of a late S wave in aV_L, a late R wave in aV_R, and a late S wave in Lead I. The absence of a late S wave in Leads V_5 and V_6 was unusual, but was probably due to the coexistent

conduction defect in the outer wall of the left ventricle. The transient reduction in the amplitude of the R wave in Leads V_5, V_6, and aV_L could have been secondary to the right bundle branch block and thus could not be accepted as evidence of a left ventricular lesion. The sudden development of right bundle branch block was suggestive of infarction of the septum, but the subsequent disappearance, together with the return to a pattern, on Jan. 29, 1944, much like that in the original tracing, raised doubt as to the cause of the right bundle branch block. It is noteworthy that the pattern on Jan. 29, 1944, was almost identical with that of October 21 except in V_3 and V_4, where the differences were attributable to a shift in transitional zone. Digitalis effects upon the RS-T segment and T wave were less marked in the last than in the first tracing.

Pathologic Findings.—The heart weighed 470 grams and exhibited on old, completely healed infarct involving the apical one-half of the anteroseptal wall of the left ventricle and the apical one-third of the lateral and posterior walls and the left side of the septum, together with a recent infarct of the basal two-thirds of the lateral wall and the interventricular septum, as outlined in Fig. 17. The old infarct had caused dense fibrosis of the subendocardial one-half of the free wall of the left apex and very patchy fibrosis of the subepicardial one-half. Thus, the findings in Leads V_5 and V_6 corresponded closely with the old infarct of the apical portion of the lateral wall, whereas those in V_3 and V_4 conformed with the anteroseptal lesion. No signs of extension into the posterior aspect of the apex were evident in Leads II, III, or aV_F, apparently because the heart was in a horizontal position. The old infarct of the apical portion of the interventricular septum was not detected electrocardiographically. The recent infarct of the basal two-thirds of the septum could have produced right bundle branch block, but the transient duration of the conduction defect made it necessary to consider a functional lesion associated with cardiac failure as an alternative possibility. The recent infarct of the basal two-thirds of the lateral wall was confined to the subendocardial one-half of the wall and was not diagnosed from the electrocardiograms of Jan. 23 and Jan. 29, 1944. It is noteworthy that this lesion caused no significant change in the QRS pattern in Leads V_5 or V_6. The high lateral infarct might have been detected if high precordial and axillary leads at the level of the third intercostal space had been taken. This case well demonstrates the inadequacy of the customary precordial leads in the diagnosis of high lateral infarction.

CASE 154.—A 48-year-old woman was first admitted in December, 1946, because of pneumonia. She gave a history of sudden onset of severe precordial pain and dyspnea in 1944 and a second attack in August, 1945, both treated by prolonged bed rest at home. Digitalis had been maintained ever since and was increased in April, 1947, because of congestive failure. Toxic psychosis developed, leading to readmission. Death occurred on the tenth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained three days before death is reproduced in Fig. 18,*A*. The QRS-T pattern in this tracing was similar to that in three previous tracings taken during the first admission. The QRS interval measured 0.12 second. The distinct Q wave and late intrinsicoid deflection in Lead V_6 aroused the suspicion of infarction of the subendocardial portion of the lateral wall, but could have been a manifestation of uncomplicated left ventricular hypertrophy. The findings in Lead aV_L were more distinctive. The Q/R ratio of 30 per cent, the notched upstroke, and the 0.075 second interval preceding the intrinsicoid deflection were representative of the type of conduction defect of the outer wall produced by patchy infarction. Although the suggestion of an initial negative phase preceding the upright P wave in aV_L would ordinarily raise the question of transmission of the potential variations of the posterobasal aspect of the heart to the left arm, the close resemblance of the P wave in aV_L to that in Lead V_6 indicated a common pathway through the lateral wall of the left ventricle. Therefore, it was concluded that the Q wave and notched upstroke in Lead aV_L were due to lateral infarction involving the subendocardial layer and distributed in a patchy manner through the remainder of the wall. This pattern carried over into Lead I, which was strongly suggestive of lateral infarction. The initial phase of the QRS complex was upright in the first five precordial leads. The decrease in the amplitude of the R wave from 10.0 mm. in V_2 and V_3 to 5.0 mm. in V_4 and V_5 raised the question of anteroseptal infarction, but might have been merely a transitional phenomenon. The depression of the RS-T junction and straightening of the segment following the tall

Ṛ wave of Leads V_6 and aV_L and the reciprocal upward displacement and straightening of the RS-T segment following the deep S wave of the first four precordial leads were attributed to the superimposed effects of full digitalization.

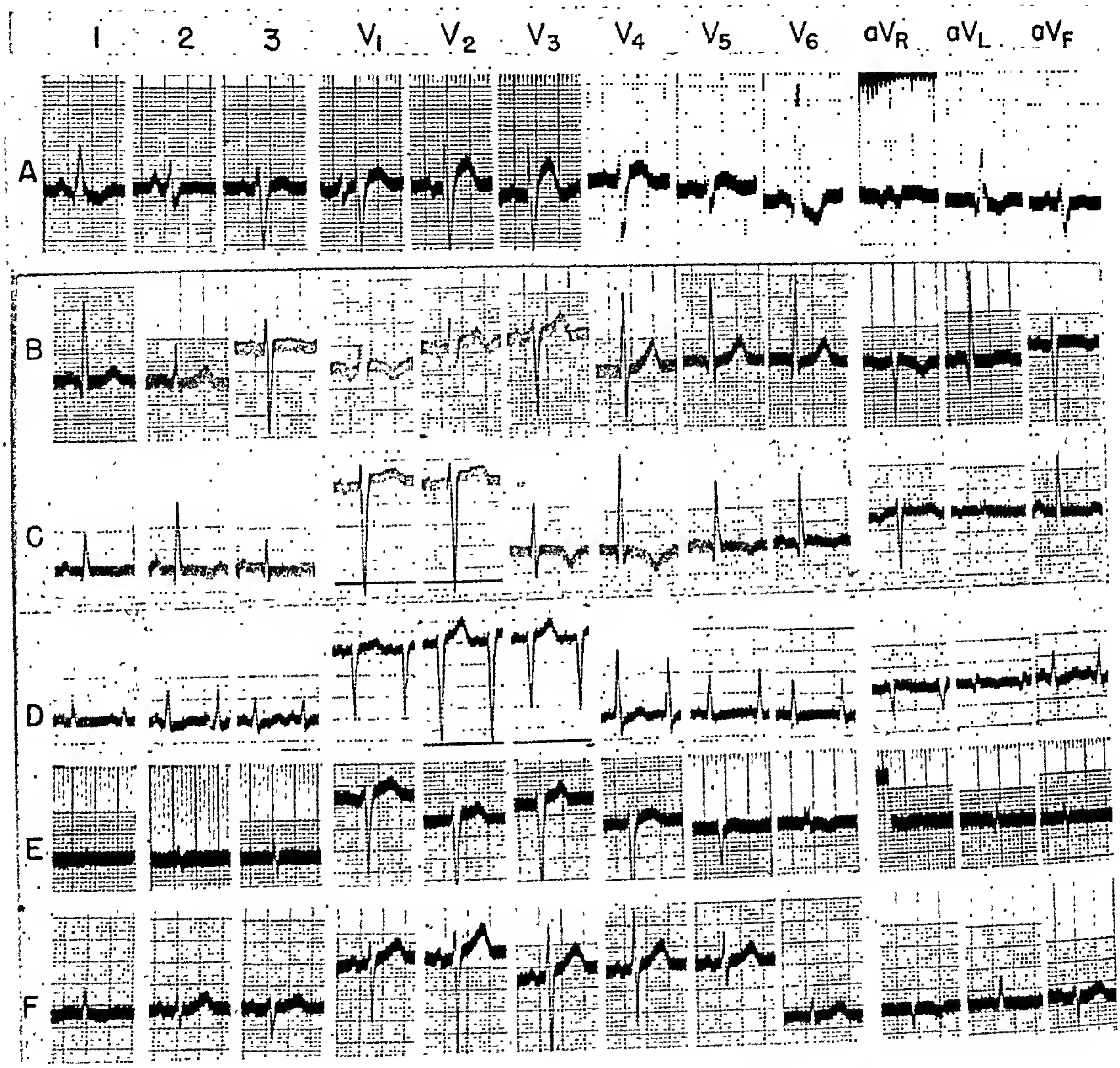

Fig. 18.—Electrocardiograms in old, healed lateral infarct. *A*, Case 154; *B*, Case 156; *C*, Case 157; *D*, Case 158; *E*, Case 160; *F*, Case 161.

Pathologic Findings.—The heart weighed 475 grams and revealed an old, completely healed lateral infarct, closely comparable in size and position to the lesion in Case 145 (Fig. 9). The resultant fibrosis was dense in the subendocardial one-fourth to one-half and very patchy in the remainder of the wall. There was good correspondence between the findings in Lead aV_L and the old, high lateral infarct at autopsy. The borderline pattern in V_6 was compatible with the thin layer of subendocardial infarction in the apical portion of the lateral wall. The continuation of the infarct into the posterior wall near the apex, in a fashion comparable to that in the second segment of Fig. 9, was not detected in Lead aV_F because of the horizontal position of the heart.

Case 155.—A 72-year-old man gave a typical history of myocardial infarction nine months prior to hospital admission. Since then he had had repeated paroxysms of nocturnal dyspnea

and had taken digitalis for three months. He was admitted in severe congestive failure and died of bronchopneumonia on the sixth day.

Electrocardiographic Findings.—An electrocardiogram was obtained thirteen hours after admission, but is not reproduced because of its close resemblance to that in Case 154 (Fig. 18,*A*). The QRS complex in Leads V_1, V_2, and V_3 was comparable to that in the corresponding leads in Case 154 and a multiphasic transitional complex was recorded in Lead V_4, resembling that in V_5 (Fig. 18,*A*). The combination of the QRS interval of 0.12 second with a QR pattern and late intrinsicoid deflection in Leads V_5, V_6, and aV_L was indicative of a conduction defect in the anterolateral wall of the left ventricle. In Lead V_5 the Q wave was only 0.02 second in duration, but was followed by coarse notching near the base of the ascending limb of the R wave and an abnormally long (0.05 second) interval from onset to peak of the R wave. In Lead aV_L a comparable notch appeared on the descending limb of the Q wave and the interval from onset to nadir of the Q wave was 0.04 second, whereas that from beginning to peak of the R wave was 0.03 second. The findings in V_6 and aV_L were regarded as different manifestations of the same lesion and were attributed to an infarct of the subendocardial portion of the anterolateral wall. The abnormal Q wave of aV_L was absent from Lead I, apparently as the result of greater initial negativity in the right arm. The T-wave pattern was comparable to that in Case 154, but the digitalis effects were not as marked.

Pathologic Findings.—The heart weighed 554 grams and exhibited an old, healed infarct of the subendocardial one-half of the anterolateral aspect of the apex, comparable in size and position to that in Case 138 (Fig. 2). Although the electrocardiograms in Cases 154 and 155 were closely comparable, the subendocardial infarct in the former case involved the entire lateral wall, but chiefly in its basal two-thirds, whereas the subendocardial infarct in this case was limited to the apical one-third. The fact that the infarct extended farther into the anterior wall of the apex in this case may have accounted for the abnormal QR pattern in Lead V_5, as well as in V_6 and aV_L.

CASE 156.—A 65-year-old man was admitted to the hospital with a history of chronic alcoholism complicated by delirium tremens. He had had intermittent retrosternal fullness for the last five months, but gave no definite history of myocardial infarction. He contracted pneumonia and died on the nineteenth hospital day. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the fourth hospital day is reproduced in Fig. 18,*B*. The initial deflection was upright in the first three precordial leads and measured 4.0 mm. in V_1 and 5.0 mm. in V_2, and decreased to 3.0 mm. in V_3. A minute Q wave of brief duration and a tall R wave were recorded in the last three precordial leads, the Q/R ratio being within normal limits. In Lead aV_L there was a Q wave 0.03 second in duration and 6.0 mm. in depth, or approximately 30 per cent of the succeeding R wave. The interpretation of the findings in aV_L depended upon the decision as to whether the potential variations of the left arm were transmitted chiefly from the lateral or from the posterobasal wall of the left ventricle. The QR complex in Lead aV_L could be considered abnormal if derived from the lateral wall, but at the upper limits of normal if transmitted from the vicinity of the posterior portion of the atrioventricular groove. The lack of a late R wave in Lead aV_R was against the latter, but the suggestion of a minute negative phase prior to the upright P wave made it impossible to definitely exclude transmission from the posterobasal wall. Therefore, the findings in Lead aV_L were regarded as strongly suggestive, but not as diagnostic, of lateral infarction. The findings in the precordial leads, when considered by themselves, were insufficient to justify a diagnosis of infarction, but in view of the interpretation of Lead aV_L, it was possible that the slight reduction in the amplitude of the R wave in V_3 and the minute Q waves in the last three precordial leads may have been the result of a small, patchy anterolateral infarct. There was no evidence in either the RS-T segment or T waves to suggest a recent lesion. The standard leads showed definite left axis deviation, but were not diagnostic of infarction.

Pathologic Findings.—The heart weighed 532 grams as a result of left ventricular hypertrophy. A patchy fibrosis was found in the subendocardial one-half of the anterolateral wall in the apical

three segments, occupying a position comparable to that of the infarct in Case 146 (Fig. 11) in the apical two segments, but more like that in Case 143 (Fig. 7) in the third segment. By microscopic examination, the lesion was believed to be the result of infarction. From the position and patchy character of the lesion, it was probably responsible for the borderline findings in the electrocardiogram.

CASE 157.—A 70-year-old man collapsed on the street and was brought to the hospital with aphasia and right hemiplegia and died of the cerebral vascular accident. Past history was unobtainable. No cardiac glycosides were given.

Fig. 19.—Roentgenogram of the injected heart in Case 157.

Electrocardiographic Findings.—An electrocardiogram obtained twenty hours after admission is reproduced in Fig. 18,*C*. The small R and deep S waves in right ventricular Leads V_1 and V_2 and the 2.0 mm. Q wave, tall R wave, and slightly delayed intrinsicoid deflection in left ventricular Leads V_4 through V_6 led to the diagnosis of left ventricular hypertrophy. Although the Q/R ratio in Leads V_4 through V_6 was in keeping with this diagnosis, the interval of 0.03 second from onset to nadir of the Q wave was longer than expected in uncomplicated left ventricular hypertrophy and was strongly suggestive of infarction of a thin layer of subendocardial muscle in the lateral wall of the left ventricle. The RS-T pattern in the last four precordial leads was atypical of left ventricular hypertrophy because of the deeper inversion of the T waves in V_3 and V_4 than in V_5 and V_6 and because of the lack of the expected RS-T depression. The RS-T pattern was compatible with involvement of the subepicardial layer secondary to infarction or localized pericarditis, but further tracings would have been needed to interpret its significance properly. The Q and notched R waves in Lead aV_L would have been strongly suggestive of lateral

infarction if it had been representative of the potential variations of the lateral wall, but the associated negative P waves suggested that cavity potentials may have had a significant effect upon the recordings in Lead aV_L. Thus, the electrocardiographic findings were very suggestive of infarction of the subendocardial portion of the anterolateral wall, but were not sufficiently marked to be pathognomonic.

Pathologic Findings.—The heart weighed 582 grams as a result of left ventricular hypertrophy secondary to aortic stenosis. An old, healed, patchy infarct was found, occupying the subendocardial three-fourths of the lateral and posterolateral walls in the apical three segments and extending into the middle zone of the posterolateral wall in the fourth and fifth segments, as outlined in Fig. 19. This infarct was probably responsible for the QR patterns in Leads V_6 and aV_L, but did not produce definite abnormalities in aV_F. Leads in the posterior axillary line and higher in the axilla might have revealed diagnostic signs. The infarct did not extend far enough forward to explain the deeply inverted T waves in Leads V_3 and V_4. These may have been secondary to the left ventricular hypertrophy or might have resulted from a histologically unrecognized anterior ischemia.

CASE 158.—A 46-year-old man had suffered from diabetes for five years and was admitted to the hospital with gangrene of the left foot. He had had exertional dyspnea for some time, but gave no definite history of myocardial infarction. Shortly after a surgical debridement, he was seized with severe retrosternal pain and dyspnea, went into shock, and died three hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained one hour after the onset of the shock is reproduced in Fig. 18,*D*. The QRS pattern was essentially the same as that in a preoperative tracing which is not reproduced. The initial deflection was upright in all precordial leads. The R wave was unusually small in Leads V_2 and V_3, and when taken in conjunction with the subsequent deep S wave, was attributable to left ventricular hypertrophy. The QRS complexes in left ventricular Leads V_4 through V_6 and aV_F were in no way suggestive of infarction. On the other hand, Lead aV_L displayed a QR complex, a slight elevation and bowing of the RS-T segment, and inversion of the T wave, suggestive of lateral infarction. This Q wave was cancelled out from Lead I because of a greater early negativity of the right arm, which was recorded as an upright deflection in Lead I. The slurring of the Q wave in aV_L and the time interval of 0.03 second from its onset to nadir constituted further evidence strongly in favor of infarction. However, it was necessary to consider vertical position with transmission of cavity potentials through the mitral orifice and atrium to the left arm as an alternative explanation for the QRS-T pattern in Lead aV_L. The fact that the P wave in Lead aV_L was isoelectric gave no help in the differentiation and left the source of the QRS-T pattern in doubt. For this reason, an unequivocal diagnosis of lateral infarction was not justified. High precordial and axillary leads were indicated, but were not obtained in this case. The preoperative tracing showed isoelectric RS-T junctions in Leads V_4 through V_6 and aV_F and a localized inversion of the T wave in Lead V_4, whereas the postoperative tracing revealed RS-T depression in Leads V_4, V_5, and aV_F and reversal in the direction of the T wave in V_4. The RS-T depression was strongly suggestive of acute left ventricular ischemia, secondary to the shock. A change from an inverted to an upright T wave is the reverse of the usual finding in ischemia, but has been observed during induced angina pectoris.[16] However, no significant change took place in the QRS-T pattern in Lead aV_L, indicating that the lateral infarct, if present, had occurred prior to hospitalization.

Pathologic Findings.—The heart weighed 358 grams and exhibited an aneurysm of the basal two-thirds of the lateral wall, secondary to an old, healed infarction, involving the entire lateral wall, and continuing slightly into the anterior and posterior walls, as demarcated by the area of avascularity in the roentgenogram (Fig. 20). Because of the size of the infarct, QRS abnormalities should have been recorded in Leads V_6 and aV_F as well as in aV_L. Microscopic blocks showed no evidence of recent infarction, but did not exclude terminal damage to the subendocardial portion of the anterolateral wall, since the three-hour interval between the onset of shock and death may have been too short for the development of histologic changes.

Fig. 20.—Roentgenogram of the injected heart in Case 158 with a large, healed lateral infarct demarcated by the avascularity and thinning of the wall.

CASE 159.—An 84-year-old woman was brought to the hospital in coma with marked peripheral circulatory collapse, an apical heart rate of 190 per minute, and signs of occlusion of the left brachial artery. Past history was unobtainable. Death occurred on the third hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained on the first hospital day revealed auricular flutter with a 2:1 ventricular response and right bundle branch block. The findings were typical of right bundle branch block in all leads except aV_L, which displayed an initial Q wave 0.03 second in duration followed by a slurred R wave. In a tracing made on the following day after the administration of 0.8 mg. of Cedilanid, auricular fibrillation had replaced flutter and the right bundle branch block had disappeared. The initial deflection was upright in all precordial leads and the QRS complexes in these leads were not remarkable in contour. In Lead aV_L the QR complex was still present and consisted of a Q wave 0.03 second in duration, 2.0 mm. in depth, and 40 per cent of the succeeding R wave. The consistently abnormal QR complex in aV_L was strongly suggestive of high lateral infarction, but the possibility of its transmission from the left ventricular cavity through the mitral orifice could not be positively excluded. The initial Q wave was obliterated in Lead I because of greater initial negativity of the right than the left arm.

Pathologic Findings.—The heart weighed 500 grams and revealed an old, completely healed and partially calcified subendocardial infarct involving the lateral wall at the base and extending backward into the posterolateral wall near the apex. The position of this infarct corresponded closely with that in Case 145 (Fig. 9), except that the involvement of the second segment of this case was comparable to that of the third segment of Fig. 9. The lesion was confined to the subendocardial one-half of the wall and showed no evidence of recent activity. This infarct ex-

plained adequately the abnormal QR pattern in Lead aV_L. The absence of diagnostic signs in Leads V_6 and V_5 was probably due to the fact that the infarct had not reached the apical segment and was confined to a small portion of the posterolateral wall in the second and third segments. Involvement of the posterolateral wall was not evident in Lead aV_F, presumably because the heart was in horizontal position.

Case 160.—A 52-year-old man gave a history of abrupt congestive failure four years previously with complete recovery. He was able to carry on normal activity until one month before hospital admission, when there was recurrence of paroxysmal nocturnal dyspnea followed by progressive edema. Thoracic pain was denied. He had been taking digitalis under the direction of his family physician, but was in advanced congestive heart failure on admission and failed to respond to therapy, expiring on the fourth day.

Electrocardiographic Findings.—An electrocardiogram obtained one hour after admission is reproduced in Fig. 18,*E*. Auricular fibrillation was present. The similarity of the RS complex in V_2, V_3, and V_4 to that in Lead V_1 indicated that all four leads were reflecting the potential variations of the right ventricle, as a result of either right ventricular dilatation or of displacement of the heart to the left. In Lead V_5, there was a barely detectable initial R wave followed by an S wave, which was notched near its termination, and in Lead V_6 there was a small, notched R wave and inverted T wave. The findings in Lead V_5 were suggestive of a small, patchy, anterolateral infarct, but might have represented a transitional zone phenomenon in a case of right ventricular dilatation. The equiphasic QR complex of aV_L was also suggestive of lateral infarction. Transmission from the posterobasal, rather than the lateral wall of the left ventricle had to be considered in the differential diagnosis, but reference of cavity potentials through the mitral orifice to the left arm could be excluded because the heart was in semihorizontal to horizontal position. From the RST-T pattern, it was believed that the patchy infarct of the anterolateral wall was old and healed.

Pathologic Findings.—The heart weighed 523 grams and exhibited both left ventricular hypertrophy and right ventricular dilatation and hypertrophy. A small, completely healed infarct was found in the subendocardial one-half of the anterolateral wall in the two apical segments and was comparable in size and position to the lesion in the two apical segments in Case 146 (Fig. 11). Although there was correspondence between the findings in Leads V_5 and aV_L and the position of the infarct at autopsy, there was uncertainty as to whether the findings in V_5 were the result of the infarct or merely a transitional zonal phenomenon.

Case 161.—An 81-year-old diabetic man had suffered from angina pectoris for three years and from intermittent claudication for five weeks. He was admitted to the hospital because of gangrene of the left leg. Amputation was performed, but death occurred on the fifth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained twenty-four hours after admission is reproduced in Fig. 18,*F*. The QRS-T complex was considered to be within normal limits in all precordial leads. The heart was in horizontal position and the T waves in Lead aV_L and Lead I were isoelectric, but the limb leads also showed no evidence of infarction.

Pathologic Findings.—The heart weighed 379 grams and exhibited a small, completely healed, patchy infarct, confined to the subendocardial one-half of the lateral wall in the apical three segments and comparable in size and position to the infarct in the corresponding segments in Case 146 (Fig. 11). There was no evidence of recent involvement. This case illustrates the fact that an infarct confined to the subendocardial portion of the lateral wall may be completely missed in the six precordial leads and in the standard and unipolar extremity leads. A clinical history of coronary disease without specific abnormalities in the routine electrocardiogram constitutes an indication for additional high axillary and precordial leads and for esophageal leads.

COMMENT

The criteria for the interpretation of the findings in Leads V_5, V_6, and aV_L have been covered in detail,[5] and the electrocardiographic patterns associated with anterolateral infarction and those of posterolateral infarction have been described in previous reports.[4,5] The correlation between electrocardiographic and pathologic findings in primary lateral infarction has been considered in individual case reports, but remains for summary. The twenty-seven cases have been classified into three groups according to the distribution of the lesion at autopsy: (A) infarction of the basal one-half of the lateral wall, continuing for a variable distance into the apical one-half (fourteen cases); (B) infarction involving chiefly the apical one-third of the lateral wall (eleven cases); and (C) infarction confined to the mid-portion of the lateral wall (two cases).

Correlation of Electrocardiographic and Pathologic Findings in Group A.—The common pathologic finding which led to the classification of fourteen cases into this group was infarction of the greater portion of the basal one-half of the lateral wall of the left ventricle and the variable features necessitating further subdivision were referable to the involvement of the apical one-half of the lateral wall, the distribution between endocardium and epicardium, and the age of the lesion. Most of these infarcts were shaped like a bullet. The base lay high in the lateral wall parallel to the atrioventricular groove, but generally separated from it by a narrow strip of intact myocardium, whereas the blunted apex usually projected into the apical one-third of the left ventricle. In three patients (Cases 144, 147, and 153) the long axis of the infarct was parallel to that of the left ventricle and the lesion spared the apical one-third or more of the lateral wall. In seven patients the infarct ran diagonally backward, terminating in the apical one-third of the posterolateral wall in five (Cases 142, 145, 152, 154, and 159), but reaching the tip of the posterolateral wall in two (Cases 151 and 158). In four patients the infarct ran diagonally forward, terminating in the apical one-third of the anterolateral wall in one (Case 143), but reaching its tip in three (Cases 146, 148, and 150). The infarct was transmural throughout in three patients (Cases 148, 151, and 158); transmural in its basal and subendocardial in its apical portion in two (Cases 142 and 146); confined to the subepicardial one-fourth of the wall in one (Case 150), and to the subendocardial one-half in the other eight patients. Electrocardiographic studies were available during the acute stage in nine patients, after healing in four (Cases 145, 154, 158, and 159), and during both stages in one (Case 151).

The lesion limited to the subepicardial layer in Case 150 was manifested by normal QRS complexes and deeply inverted T waves in leads from the left side of the precordium. The electrocardiographic findings were typical of pericarditis and thus conformed closely with the pathologic findings.

In the remaining thirteen patients, the infarct involved the subendocardial layer of most of the basal one-half and at least a portion of the apical one-half of the lateral wall and should have been manifested by an abnormal Q-wave pattern in overlying leads. However, no Q waves were recorded in either Lead

V_5 or V_6 in six patients; relatively small Q and tall R waves more in keeping with left ventricular hypertrophy were found in three; and abnormal Q waves were present in one or both leads in only four (Cases 142, 151, 152, and 153). The Q waves in Leads V_5 and V_6 in Cases 152 and 153 were attributable exclusively to a separate healed infarct of the anterolateral aspect of the apex found at autopsy, since they were present in tracings taken two months before the advent of the large, terminal lateral infarct and were unchanged in tracings taken subsequent to its development. Moreover, the fact that serial tracings in Case 142 showed no changes in the QRS-T pattern in Leads V_5 and V_6 suggested that the abnormalities in these leads were due to the healed anteroapical infarct found at autopsy rather than to the recent extensive lateral infarct. This left only one patient (Case 151) in whom an abnormal Q wave in Lead V_6 was referable to primary high lateral infarction. Even in this case, however, the QR complex in Lead V_6 was considered diagnostic only in the first tracing, taken soon after the development of the lesion, and could merely be regarded as suspicious of lateral infarction in subsequent tracings taken after healing.

The rarity of abnormal Q waves in Leads V_5 and V_6 in association with infarction involving most of the basal one-half of the lateral wall and extending into a portion of the apical one-half stands in striking contrast to our previous demonstration of abnormal Q waves in one or both of these leads in fifty of fifty-seven patients with evidence of pathologic infarction involving the apical one-third or more of the anterior and lateral walls of the left ventricle.[4] These Q waves could be correlated with infarction of the apical one-third of the anterolateral and lateral walls, since lesions limited to the anteroseptal portion of the apex did not produce abnormal Q waves in Leads V_5 and V_6 unless there was marked clockwise rotation of the heart.[17] The lack of diagnostic Q-wave patterns in Leads V_5 and V_6 was probably due to the tendency of high lateral infarcts to spare the apical one-third of the anterolateral wall. The lesion extended through the anterolateral wall to reach its tip in only two of the thirteen patients (Cases 146 and 148). The registration of initial R, rather than Q waves in Leads V_5 and V_6 of both patients may have been due to the short interval between the onset of the infarcts and recording of the electrocardiograms.[4] However, the presence of Q waves in more medial leads in the latter case suggested an additional factor which will be discussed.

QRS-T abnormalities sufficient to arouse the suspicion of anteroseptal infarction or to lead to its ante-mortem diagnosis were found in one or more of the first four precordial leads in five patients (Cases 143, 144, 146, 147, and 148) in which autopsy revealed infarction of the lateral or anterolateral wall, but not of the septum nor adjoining anterior wall. Despite the absence of histologic changes in the anteroseptal wall in Case 146, the occlusion near the mouth of the anterior descending coronary artery suggested that sufficient anteroseptal ischemia might have been present to have accounted for the marked RS-T depression, with normal initial R waves in Leads V_1 through V_4. A comparable RS-T depression in the same leads in Case 148 was associated with absence of the R wave from these leads and hence was not explained fully by the hypothesis of a histologically unrecognizable anteroseptal ischemia. It is possible that the

abnormalities in Leads V_1 through V_4 were due to precordial transmission of the potential variations of the large infarct of the anterolateral and lateral walls. The acutely inverted T waves in Leads V_2 and V_3 of the tracing of June 4, 1946, in Case 151 probably reflected the altered repolarization of an ischemic zone beyond the border of the high anterolateral infarct subsequently demonstrated at autopsy.

More decisive evidence of the transmission of the potential variations of the basal portion of the lateral wall to the precordium was obtained in Case 144. A QR pattern diagnostic of infarction was found localized to precordial Positions 3 and 4, not only in the customary precordial leads, but also in those taken at the level of the third intercostal space. The Q wave was much deeper and the Q/R ratio much greater in the high than in the low chest leads. In the antemortem interpretation, these findings were attributed to a subendocardial anteroseptal infarct, maximal at the base and diminishing toward the apex, but at autopsy the infarct was localized to the subendocardial portion of the basal one-half of the lateral wall and did not extend into the anterior wall. Transmission of the potential variations of the epicardial surface of the lateral wall to the precordium was apparently facilitated in this case by marked counterclockwise rotation of the heart. The combination of counterclockwise rotation and displacement of the transitional zone to the right in Case 143 may have permitted transmission of the potential variations of the infarcted basal portion of the anterolateral wall far enough to the right to explain the QR pattern in Leads V_1 and V_2. In Case 147 an abnormal QR complex was also recorded in Lead V_1 and a comparable lesion of the basal portion of the anterolateral wall was demonstrated at autopsy, but no evidence was found of the type of cardiac rotation present in Cases 143 and 144. Since no other cause for the QR pattern in V_1 was found, it was tentatively attributed to the infarct by the process of exclusion.

In one additional patient from Group B (Case 60), much deeper and broader Q waves were recorded in Leads V_3 and V_4 than in V_5 and V_6, despite the fact that the infarct involved the apical one-third of the lateral wall and only the apical 1.0 cm. of the anteroseptal wall. The lateral infarct was manifested by electrocardiographic signs of anteroseptal infarction in this case, as in Case 144, because of marked counterclockwise rotation which facilitated transmission of the potential variations of the lateral wall of the left ventricle to the precordium. The situation in these cases was opposite to that in Cases 67 and 68 where QS complexes in Leads V_5 and V_6 were attributable to the transmission of the potential variations of an infarcted anteroseptal wall to the axilla, as a result of marked clockwise rotation of the heart.

The findings in Lead aV_L were more distinctive than those in the precordial leads, QR patterns being recorded in aV_L in eleven of the thirteen cases. The minute, multiphasic QRS complex in one of the two remaining patients (Case 146) was probably transmitted from the epicardial surface covering the anterior end of the interventricular septum, as a result of clockwise rotation of the heart into a semivertical position. The initial R wave in Lead aV_L of the other patient (Case 148) was subject to the same explanation as its counter-

part in Lead V_6. The QR pattern in Lead aV_L was considered diagnostic of lateral infarction in Case 154 because of the notching and prolongation of the upstroke of the R wave, and in Case 152 because of the nature of the change from preceding tracings; whereas the QR pattern in Cases 142, 145, 147, 158, and 159 was regarded as strongly suggestive, but not quite pathognomonic, either because of low voltage or because of an element of uncertainty as to its source. The QR pattern in Lead aV_L in Cases 143, 144, and 151 was suspicious of lateral infarction, but was more likely due to left ventricular hypertrophy, whereas that in Case 153 was also suggestive, but was of indeterminate significance because of associated right bundle branch block. In three of the seven patients with findings in Lead aV_L regarded as diagnostic or strongly suggestive of lateral infarction, Leads V_5 and V_6 displayed initial R waves, and in two others, Leads V_5 and V_6 showed QR deflections more in keeping with left ventricular hypertrophy. Thus, lateral infarction may be manifested by signs in Lead aV_L, but not in the customary precordial leads.

Standard Lead I was not an adequate substitute for Lead aV_L, since Lead I revealed an initial upstroke in five of the eleven patients with QR patterns in aV_L which were either diagnostic, strongly suggestive, or suspicious of infarction. The reason for this discrepancy is that Lead I records the potential differences of the two upper extremities, whereas Lead aV_L records chiefly the potential variations of the left arm. A Q wave in Lead aV_L was not carried over into Lead I when there was greater early negativity in the right than the left arm, as evidenced by a deeper initial downstroke in Lead aV_R than in aV_L.

From this small series of cases of high lateral infarction, it would appear that Lead aV_L usually yields signs which are at least suspicious of the lesion, but seldom furnishes evidence which may be regarded as pathognomonic. The presence of signs suggestive of infarction in the customary precordial or left arm leads, as emphasized by the Wilson group,[13,14] constitutes an indication for supplementary leads higher in the precordium and axilla. The same criteria were used tentatively for the interpretation of the findings in high precordial and axillary leads taken at the horizontal level of the sternal terminus of the third intercostal space as for the corresponding official precordial lead located in the same vertical plane. However, a revision may be necessary upon completion of a current study of normal variations in the findings in these leads.

The value of high precordial leads is well illustrated by Case 145. The customary precordial leads in this case yielded evidence which was regarded as only slightly suspicious of infarction, whereas Lead aV_L displayed a QR complex that was strongly suggestive, but not diagnostic, of lateral infarction. The demonstration of an abnormal QR complex localized to a lead from the anterior axillary line at the level of the third intercostal space was considered diagnostic of high lateral infarction and was subsequently correlated with a lesion of the subendocardial one-half of the lateral wall at autopsy. An abnormal QR complex was recorded in a lead high in the mid-axilla in Case 151 after diagnostic signs had disappeared from tracings at the sixth precordial position. This conformed with the pathologic findings of more extensive infarction in the basal than in the apical one-half of the lateral wall. More marked QR abnormalities

in high than in the customary precordial leads in Case 144 could be correlated with a lesion limited to the basal one-half of the wall. The opposite finding of more marked QR abnormalities in V_5 and V_6 than in high axillary leads was encountered in Case 46 and corresponded with infarction which involved chiefly the apical one-half of the lateral wall at autopsy.

The experience with high precordial leads in the foregoing cases and in a larger group that did not come to autopsy has warranted a more extensive study to determine their value and limitations in the detection of high anterior and lateral infarcts and in the delineation of the upper boundaries of apical infarcts. Accordingly, leads at the intersection of a horizontal line through the sternal terminus of the third intercostal space with lines in the vertical plane of precordial Positions 3, 4, 5, and 6 are now being taken routinely in this clinic along with Leads V_1 through V_6.

Correlation of Electrocardiographic and Pathologic Findings in Group B.—The common pathologic finding which led to the classification of eleven patients into this group was infarction of the apical one-third of the lateral wall. The lesion was large in two patients, involving the apical two-thirds of the lateral wall in Case 141 and the apical one-half to two-thirds of the lateral and posterolateral walls in Case 157. The involvement of the lateral wall was limited to the apical one-third or, at the most, to the apical one-half in the remaining nine patients (Cases 17, 60, 138, 139, 140, 155, 156, 160, and 161). In Case 17 the infarct covered the apical one-third of the anterolateral and anteroseptal walls; in Cases 60, 138, 139, 140, and 155 the lesion occupied the apical one-third of the lateral wall, but continued into the anteroseptal portion of the extreme apex; in the remainder it was confined to the lateral wall. The infarct was transmural in Case 141, in part transmural and in part subendocardial in Case 17, dense in the subendocardial one-half and patchy in the outer one-half in Cases 60, 139, and 157, subendocardial to mid-zonal in Cases 138 and 140, and confined to the subendocardial one-half in the remainder. Electrocardiographic studies were available during the acute stage in four of the patients (Cases 60, 138, 139, and 140) and only after healing in the other five.

Abnormal Q waves diagnostic of infarction were present in Lead V_5 or in both V_5 and V_6 in five patients (Cases 17, 60, 139, 141, and 155), and QRS changes somewhat suggestive of infarction were found in these leads in three others (Cases 156, 157, and 160). Lead aV_L also showed a QR complex diagnostic of infarction in Cases 17, 141, and 155, and QRS changes strongly suggestive of infarction in Cases 60, 156, 157, and 160. Thus, QR patterns diagnostic, or at least strongly suggestive, of infarction were present in Leads V_5, V_6, and/or aV_L in eight of the eleven patients with infarction of the apical one-third of the lateral wall. On the other hand, in Case 161 there were no signs in the electrocardiogram to arouse the suspicion of the healed, patchy, subendocardial infarct found at autopsy in the apical one-half of the lateral wall.

The electrocardiographic findings in the two remaining patients (Cases 138 and 140) conformed more or less to the pattern described by Wood, Wolferth, and Bellet.[8] The marked RS-T depression and T-wave inversion in Leads V_4, V_5, and V_6 of both patients corresponded closely with the pathologic dem-

onstration of acute infarction which occupied the subendocardial layer and mid-zone of the apical one-third of lateral and anterolateral walls, respectively, but spared the subepicardial layer throughout. The absence of abnormal Q waves from Leads V_4, V_5, and V_6 of both patients was explained by the fact that the lesion in the anterolateral and extreme anterior aspects of the apex was located principally in the mid-portion of the wall and spared enough of the subendocardial muscle so that the onset of activation was not delayed.

The first electrocardiogram in Case 139, taken four and one-half hours after the onset of the pain, showed normal R waves and marked RS-T depression in Leads V_4, V_5, and V_6, whereas a second electrocardiogram, taken forty-four hours later, showed significant reduction in the initial R wave of V_4 and V_6 and a QR complex in Lead V_5 that conformed closely with the relatively small subendocardial anterolateral infarct found at autopsy. Thus, the pattern of Wood, Wolferth, and Bellet[8] may be observed as an early, but transient finding referable to acute ischemia or to early subendocardial infarction which has not progressed to the point of obliterating the response to the activating impulse.

Correlation of Electrocardiographic and Pathologic Findings in Group C.—A small, thin, subendocardial infarct confined to the middle one-third of the lateral wall was found in Cases 4 and 149. The electrocardiographic findings in both cases were consistent with the pattern of Wood and associates,[8] but those in Case 149 could have been due to a combination of left ventricular hypertrophy and digitalis action. The absence of Q waves from Leads V_5 and V_6 could be explained by the small size of the infarct and the probability that the potential variations of the overlying epicardium were referred higher in the axilla than precordial Positions 5 and 6. The fewer the number of precordial leads taken, the smaller the chance of placement of the electrode over the central or marginal zone of moderate sized infarcts. Thus, in patients with relatively small infarcts of the anterior or lateral aspects of the apex, the use of six precordial leads (V_1 through V_6) may uncover a localized abnormal Q wave diagnostic of the lesion, whereas the employment of only one or two leads may yield no signs or may show RS-T abnormalities without QRS changes. In patients with relatively small infarcts situated high in the anterior or lateral wall, supplementary high precordial or axillary leads may reveal diagnostic Q waves when the customary six precordial leads are unrevealing or show isolated RS-T abnormalities. Thus, the registration of patterns like that of Wood, Wolferth, and Bellet[8] should constitute an indication for additional exploratory leads in an effort to demonstrate QRS abnormalities more definitely diagnostic of infarction.

SUMMARY

Infarction of the lateral wall of the left ventricle was demonstrated pathologically in 105 cases, which represents an incidence of 65 per cent in a series of 161 cases. The cases of anterolateral infarction and those of posterolateral infarction have been analyzed in previous reports and the present study was concerned with a correlation of electrocardiographic and pathologic findings in twenty-seven cases of primary lateral infarction. These cases were classified into three groups,

according to the distribution of the lesion at autopsy: (A) high, (B) low, and (C) *midlateral infarction*.

A. High lateral infarction, involving chiefly the basal one-half of the lateral wall, but continuing for a variable distance into the apical one-half, was found in fourteen cases. The infarct was limited to the subepicardial layer in one case and was manifested by normal QRS complexes and deeply inverted T waves typical of the findings in pericarditis. Despite the fact that the high lateral infarct was transmural in five cases and subendocardial in the other eight, it was manifested by a diagnostic QR pattern in Lead V_5 or V_6 in only one case. The rarity of abnormal Q waves in Leads V_5 and V_6 of this group contrasted sharply with their frequency in association with infarction of the apical one-third of the anterolateral wall and was ascribed to the fact that high lateral infarcts generally spared most or all of the apical one-third of the anterolateral wall. On the other hand, Lead aV_L yielded a QR pattern which was considered diagnostic of lateral infarction in two cases, strongly suggestive in five cases, and suspicious in four cases. Standard Lead I was not an adequate substitute for Lead aV_L because it failed to show an initial downstroke in five of the eleven patients with Q waves in aV_L, because of greater initial negativity of the right than the left arm. Signs suggestive of infarction in the customary precordial or left arm leads constitute an indication for exploration of the upper precordium and axilla. Leads at the intersection of a horizontal line through the sternal terminus of the third intercostal space with vertical lines in the plane of precordial Positions 3, 4, 5, and 6 were obtained on four patients who were followed to autopsy. In one case, the findings in the customary precordial leads were equivocal, those in Lead aV_L were strongly suggestive, but those in the high precordial leads were pathognomonic of the high lateral infarct found at autopsy. The findings in the high precordial leads taken in conjunction with those in the customary leads in the other three cases aided in establishing the diagnosis and in localizing the position of the infarct.

B. Low lateral infarction was found in eleven cases and was largely or entirely confined to the apical one-third of the lateral wall in eight of these. Abnormal Q waves diagnostic of infarction were present in Lead V_5, V_6, and/or aV_L in five cases, and strongly suggestive QR patterns were found in three others. The electrocardiogram was negative in one case and conformed to the pattern of Wood, Wolferth, and Bellet in the other two cases. The RS-T depression in V_4, V_5, and V_6 could be correlated with acute infarction which involved the subendocardial and mid-zones, but spared the subepicardial layer, and the absence of Q waves was explained by the patchy character of the subendocardial lesion. A similar pattern was recorded in an electrocardiogram taken four and one-half hours after the onset of the pain in one other case, but was subsequently replaced by a QR complex diagnostic of the subendocardial infarct found at autopsy.

C. Small mid-lateral infarcts, involving the subendocardial layer of the middle one-third of the lateral wall, were found in two cases. A pattern resembling that of Wood, Wolferth, and Bellet was found in both cases, but could have been produced by a combination of left ventricular hypertrophy and

digitalis action in one of these. The absence of Q waves may have been due to the small size of the lesion and the failure to take high axillary leads.

QRS-T abnormalities in one or more of the first four precordial leads, which were suggestive of anteroseptal infarction, but were actually a manifestation of the lateral infarction, were found in five cases. Transmission of the potential variations of the infarcted lateral wall to the precordium was facilitated by marked counterclockwise rotation in three of these cases. This situation was the opposite of that in previously reported cases where abnormal Q waves were recorded in Leads V_5 and V_6 as a result of clockwise rotation sufficient to cause reference of the potential variations of an infarcted anteroseptal wall to the axilla.

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EFFECT OF POTASSIUM ON DOWNWARD T WAVES OF PRECORDIAL LEADS OF NORMAL CHILDREN

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DOWNWARD T waves occur normally in the precordial leads of children.[1,2,3] In a previous paper[3] we pointed out that these downward T waves were limited to precordial leads which showed an RS pattern. In this paper, we shall describe the mechanism probably responsible for these downward T waves.

MATERIAL AND METHOD

Ten normal white and Negro children were studied. These were selected by the following process of elimination. Multiple precordial leads were taken at random on children from the surgical ward of Lincoln Hospital. The children were convalescing from traumatic conditions, such as fractures, and from minor surgical procedures. Their ages ranged from 3½ to 12½ years. Only those children who showed downward T waves in more than one precordial lead were used in this study.

In all cases the three standard leads, the three augmented unipolar extremity leads,[4] and six unipolar precordial leads[4,5] were taken. Tracings were taken before and one hour after the child drank a solution containing 5.0 Gm. of potassium salts. The solution contained equal amounts of potassium acetate, potassium bicarbonate, and potassium citrate. One dram of solution contained 1.0 Gm. of the salts.

RESULTS

Figs. 1, 2, and 3 show typical changes in the precordial leads which were produced by potassium. It is to be noted that all of the downward T waves became upward in the precordial leads of Figs. 2 and 3 and in all of the precordial leads except V_1 in Fig. 1. A downward T in Lead V_1, however, is not abnormal, even in adults.

One child showed downward T waves in precordial Leads V_1, V_2, V_3, V_4, and V_5 in the control tracings (Fig. 1). In this case, potassium caused the T waves to become upward in all these precordial leads except V_1.

One child showed downward T waves in Leads V_1, V_2, V_3, and V_4 in the control tracings (Fig. 4). Potassium caused the T wave in Lead V_4 to become

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upright; the T wave in Lead V_3 became biphasic and in Leads V_1 and V_2 the T waves became more downward. This apparently paradoxical effect of potassium is explained in the discussion.

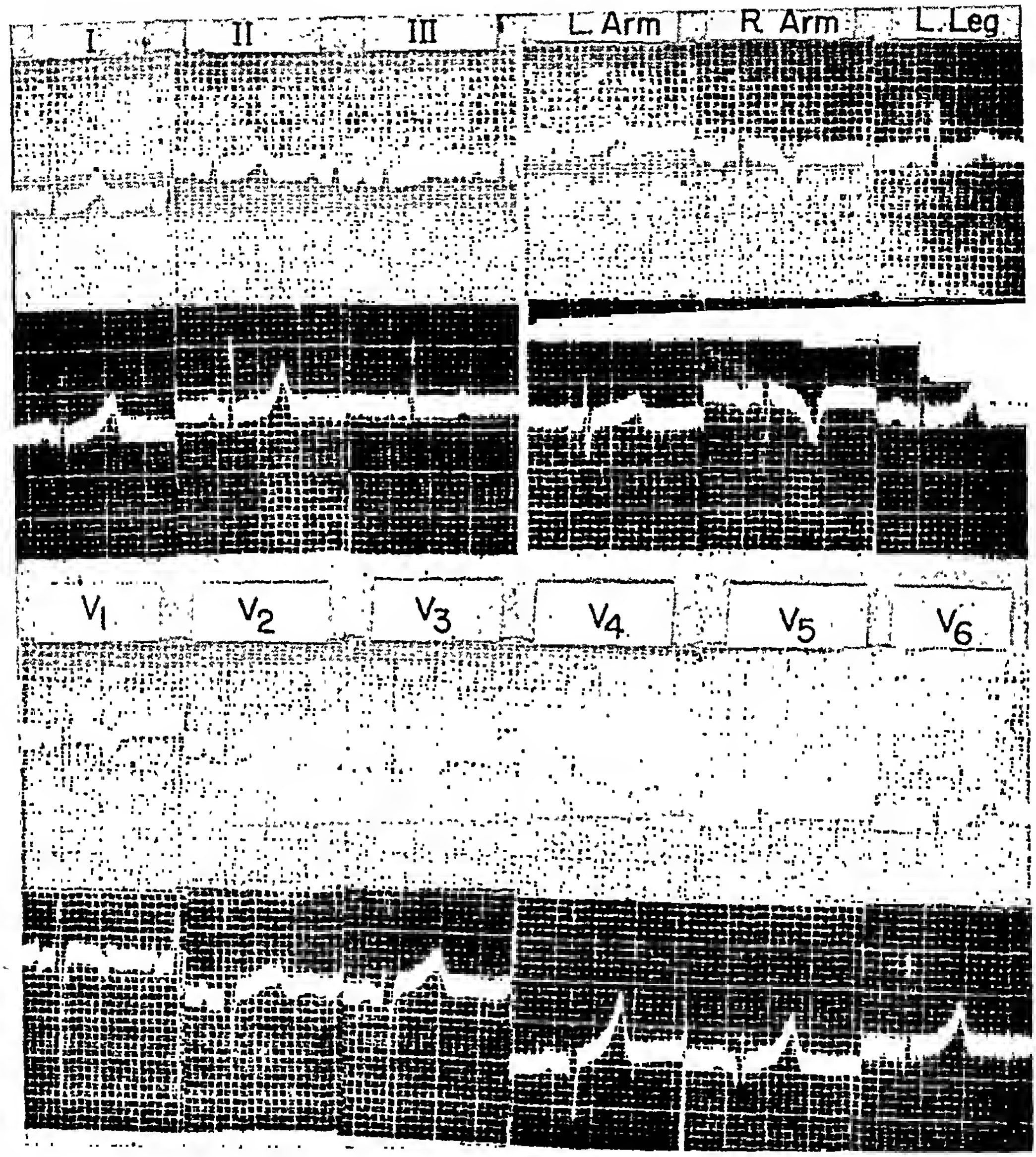

Fig. 1.—Tracings of a normal 5½-year-old white girl. Upper rows, control tracings. Lower rows, tracings taken one hour after the child drank a solution containing 5.0 Gm. of potassium salts.

Four children showed downward T waves in Leads V_1, V_2, and V_3 in the control tracings. Potassium caused the T waves to become upright in Leads V_2 and V_3 in three patients. In one child, a 12½-year-old boy, the T waves remained downward but became smaller.

Four children showed downward T waves in Leads V_1 and V_2 in the control tracings (Figs. 2 and 3). Potassium caused the T waves to become upright in

both leads in two cases and caused the T wave in Lead V_2 to become upright in two cases.

Potassium not only tended to make downward T waves in precordial leads become upright, but it also tended to make the upward T waves become taller and show a sharp peak (Figs. 1, 2, 3, and 4).

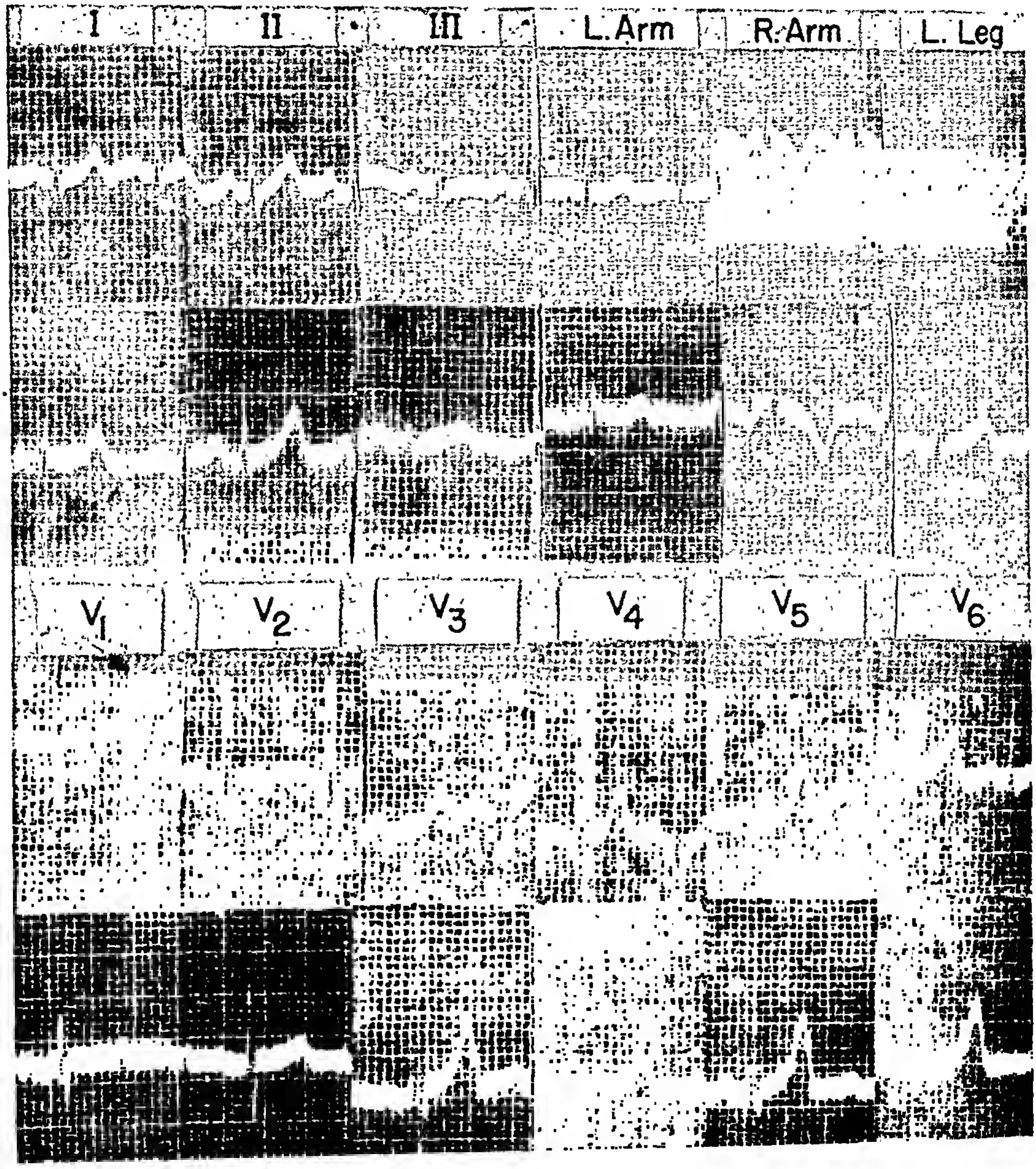

Fig. 2.—Tracings of a normal 9-year-old white girl. See legend of Fig. 1.

Other Electrocardiographic Changes.—In the unipolar extremity leads and standard leads, the direction of T did not change after potassium, but downward T waves usually became deeper and peaked, and upward T waves became taller and peaked (Figs. 1, 2, 3, and 4).

Potassium caused no significant changes in the P waves, P-R intervals, QRS complexes, Q-T intervals, and RS-T segments.

DISCUSSION

It is well known that the administration of potassium salts tends to make the T waves tall and peaked in the standard leads.[6] Similarly, patients with diseases associated with high blood potassium levels show tall, peaked T waves.[7] When the blood potassium level is low, the T waves become low or even inverted.[8] In such cases, the administration of potassium salts causes the T waves to become upright.[9]

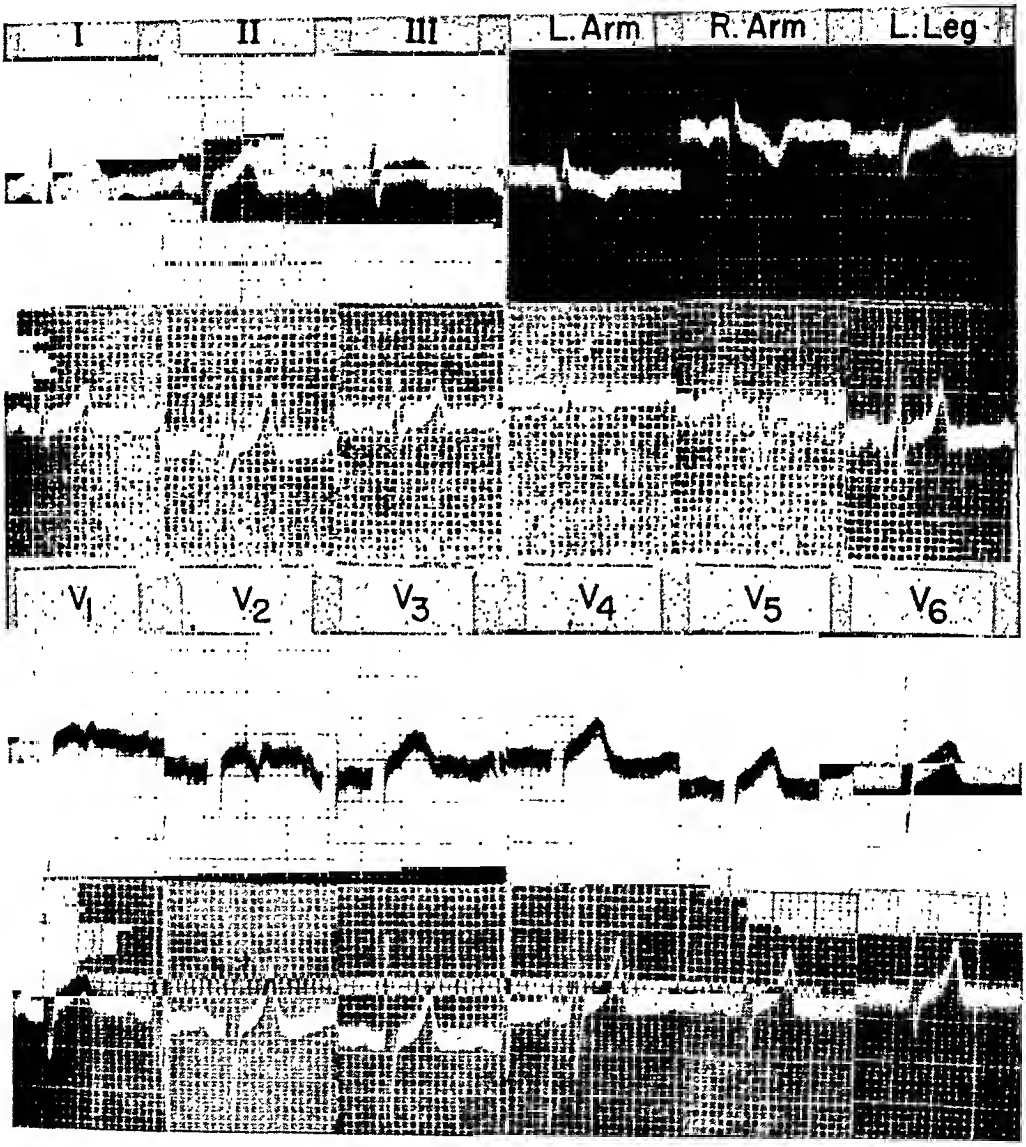

Fig. 3.—Tracings of a normal 4-year-old white boy. See legend of Fig. 1.

Our observations are of interest in that the downward T waves whose direction was reversed by potassium were localized to precordial leads. In this connection we can analyze the unusual effects of potassium shown in Fig. 4. It has been pointed out elsewhere[10] that the pattern of a unipolar lead depends

upon the surface of the heart which the lead faces. Unipolar precordial leads usually face either the epicardial surface of the right ventricle or the epicardial surface of the left ventricle. A unipolar precordial lead that faces the epicardial surface of the right ventricle shows an RS pattern with an upright or inverted T wave.[3,10] A unipolar precordial lead that faces the epicardial surface of the left ventricle shows a qR pattern and an upward T. Thus, the downward T

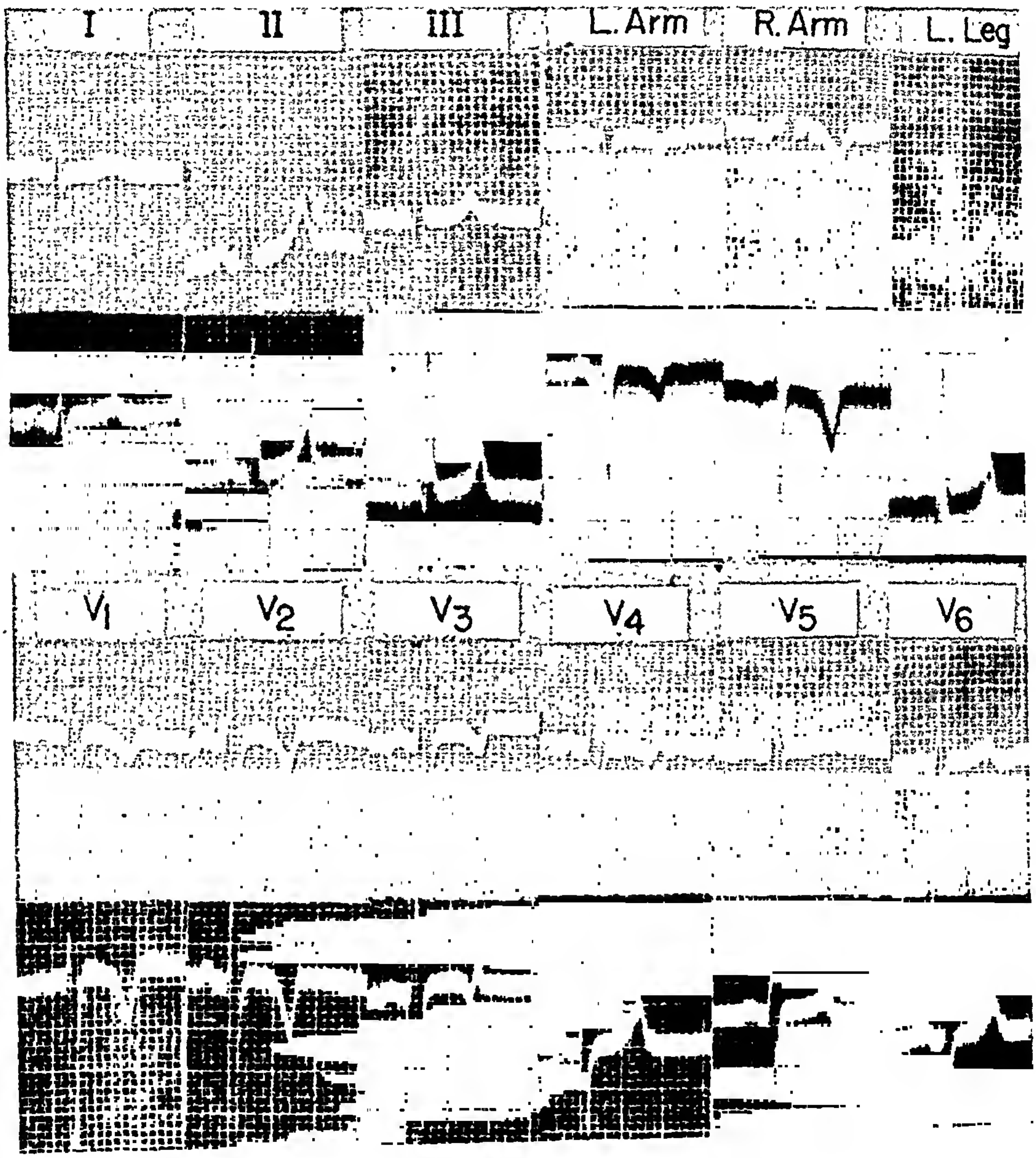

Fig. 4.—Tracings of a normal 11-year-old white boy. See legend of Fig. 1.

waves of the precordial leads of children are found in leads over the right ventricle.[3] However, the wall of the right ventricle barely extends beyond the right border of the sternum. Thus, Lead V_1 which is taken with the electrode to the right of the sternum tends to overlie the right auricle and face the cavity of the right ventricle. Leads that face the cavity of the right ventricle show an RS pattern and a downward T wave. Normally the unipolar right arm lead faces

the right ventricular cavity. Potassium in all our cases caused the T in the right arm lead to become deeper (Figs. 1, 2, 3, and 4). Therefore, if a precordial lead near the sternum were to face the cavity of the right ventricle rather than the epicardial surface of the right ventricle, T should become deeper after the administration of potassium. If clockwise rotation of the heart around its long axis were also present, the right ventricle would move toward the left and precordial Lead V_2 would also tend to face the right ventricular cavity in addition to Lead V_1.

Thus, in Fig. 4, if we assume that clockwise rotation of the heart around its long axis is present, Leads V_1 and V_2 would face the cavity of the right ventricle, just as the unipolar right arm lead does, and potassium should cause the T waves of all these leads to become deeper. This does occur. Evidence that clockwise rotation of the heart in Fig. 4 exists consists of the fact that precordial Lead V_6, which ordinarily faces the epicardial surface of the left ventricle, shows an RS pattern, indicating that it is facing the epicardial surface of the right ventricle because of clockwise rotation.[10,11]

This observation also helps to explain the fact that in eight of our ten cases, the downward T wave of Lead V_1 remained downward after potassium. However, in only two cases did the T wave in Lead V_1 become deeper; in six cases it became smaller. Possibly if we had given a larger dose of potassium in these six cases, the T would have become upward in Lead V_1 just as it did in Fig. 3.

The effect of potassium in reversing the downward T waves of precordial leads that face the epicardial surface of the right ventricle in children suggests that these downward T waves may be due to the fact that the right ventricular muscle contains less potassium than the muscle of the left ventricle. Exact proof of this by means of chemical analysis is, however, extremely difficult, if not impossible.

CONCLUSIONS

Normal children frequently show downward T waves in precordial leads which are taken near the sternum and which show an RS pattern. These downward T waves occur in leads that face the right ventricular cavity or the epicardial surface of the right ventricle. The administration of potassium salts causes the downward T waves of precordial leads that face the epicardial surface of the right ventricle to become upright. The T waves of precordial leads that face the cavity of the heart, such as Lead V_1 and rarely Lead V_2, may become deeper after potassium. Potassium makes upward T waves in precordial leads taller and peaked. In the unipolar extremity leads and standard leads, potassium does not change the direction of the T waves but makes upward T waves taller and peaked and downward T waves deeper and peaked.

ADDENDUM

Normal Negro adults frequently show downward T waves in precordial leads, similar to children. We have been able to cause these T waves to become upward by the administration of 10 Gm. of potassium salts. These observations will be reported elsewhere in detail.

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AURICULAR PAROXYSMAL TACHYCARDIA IN ASSOCIATION WITH MYOCARDIAL INFARCTION

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SUPRAVENTRICULAR tachycardia is extremely rare in association with myocardial infarction. Its frequency is suggested by its numerical relationship to auricular fibrillation, auricular flutter, and ventricular paroxysmal tachycardia. In the records of 1,247 patients in whom definite proof of myocardial infarction was found at the Los Angeles County Hospital, auricular fibrillation was observed in eighty-four patients,[1] auricular flutter in twenty,[2] ventricular paroxysmal tachycardia in fourteen, and supraventricular tachycardia in only five. Rosenbaum and Levine[3] in a study of 208 patients believed to have had their first attack of myocardial infarction found no instances of auricular paroxysmal tachycardia. Mintz and Katz[4] mention three instances in a group of 572 patients. Master, Dack, and Jaffe[5] verified supraventricular paroxysmal tachycardia by electrocardiograms in five of 300 patients who had myocardial infarction. This report is based upon the records of five patients observed in the Los Angeles County Hospital who were considered to have supraventricular tachycardia.

CASE REPORTS

CASE 1.—P. F. (No. 743-128), a Negro man 56 years of age, was admitted to the Los Angeles County Hospital on Oct. 7, 1941, because of a recent myocardial infarction. In electrocardiograms taken Oct. 8 and Nov. 26, 1941, there were indications of the expected serial changes of an anterior myocardial infarction (Fig. 1). He was discharged on Dec. 11, 1941.

On Dec. 18, 1941, he was readmitted because of increasing dyspnea, a swollen abdomen, and swelling of the ankles. There was a systolic murmur which was estimated as being of Grade 4 intensity. The liver extended 5.0 cm. below the right costal margin. The lower extremities were edematous to the mid-thighs. Digitalis was given, grains 3 of the powdered leaf three times daily for three days, and then grains 1½ daily. The electrocardiogram on December 19 showed no new changes in the pattern. He was discharged on Jan. 1, 1942, and was continued on digitalis, grains 1½ daily.

He was readmitted on Feb. 9, 1942. He had had almost constant pain in the upper right chest since his latest discharge and had had hemoptysis on two or three occasions. On the morning of Feb. 9, 1942, he suffered severe crushing, vise-like pains over the upper sternum. He was admitted at this time in shock; the blood pressure was 110/90 and the pulse was rapid and irregular with a rate of approximately 160 per minute. An electrocardiogram taken on February 9 revealed supraventricular tachycardia with changes consistent with another infarction. Evidence of

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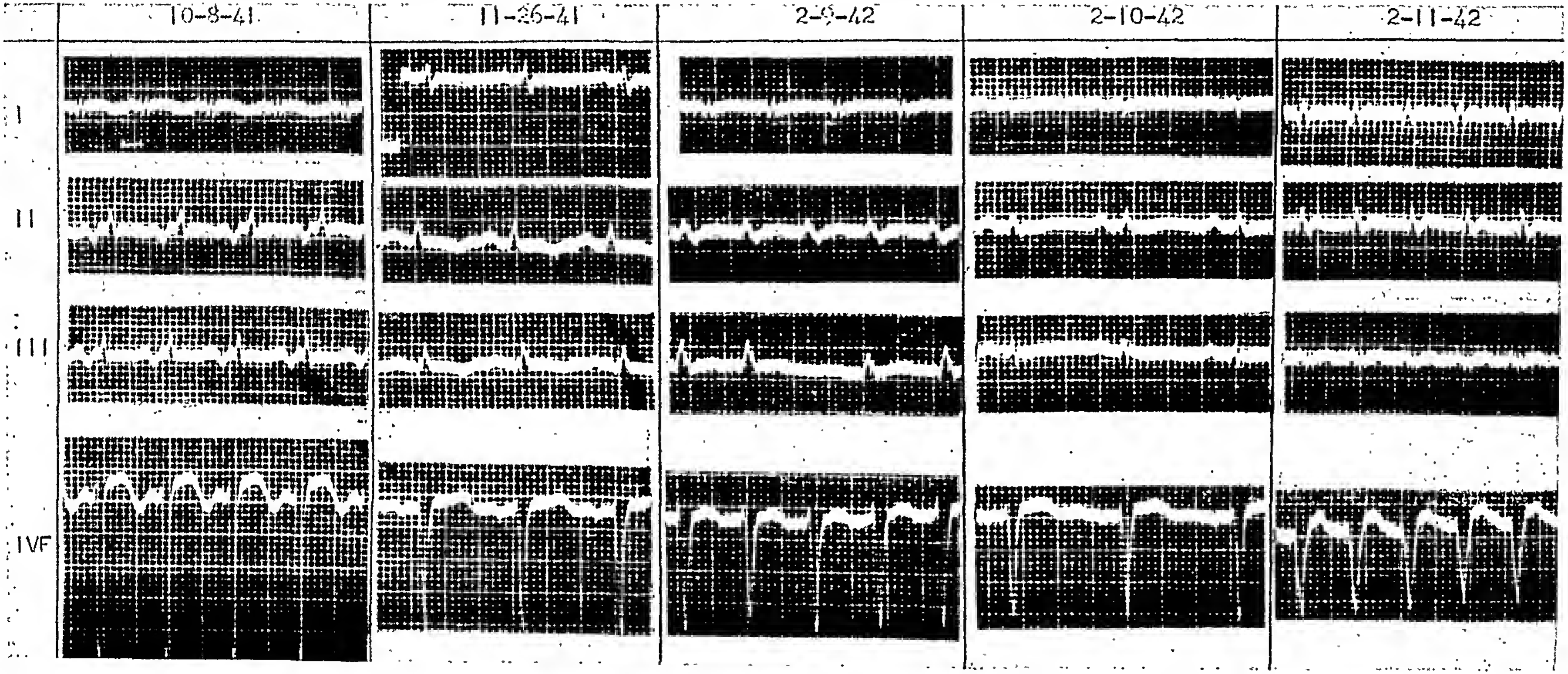

Fig. 1.—Case 1. Oct. 8, 1941, and Nov. 26, 1941: Anterior myocardial infarction.

Feb. 9, 1942: Supraventricular tachycardia. Auriculoventricular block, Lead III.
Feb. 10, 1942: Sinus rhythm.
Feb. 11, 1942: Supraventricular tachycardia.

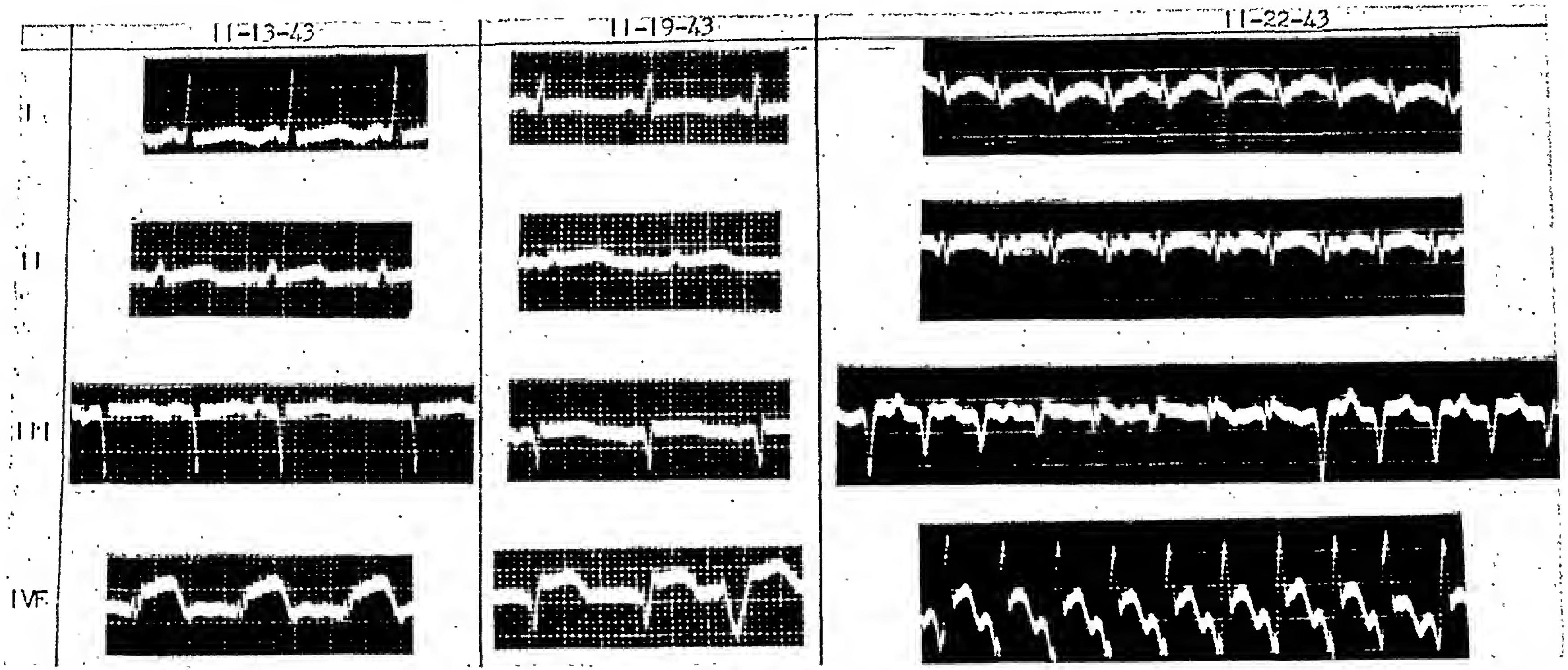

Fig. 2.—Case 2. Nov. 13, 1943: Anterior myocardial infarction. Auricular premature beat, Lead III.

Nov. 19, 1943: Anterior myocardial infarction. Ventricular premature beat, Lead IVF.
Nov. 22, 1943: Supraventricular tachycardia.

atrioventricular block was observed at several points in the tracing. No digitalis was given on February 9. On February 10, the electrocardiogram showed sinus rhythm. Digitalis, grains 3, was given on February 10 because of "increasing basal râles." The next morning, February 11, the tachycardia returned and the electrocardiogram revealed the existence of auricular paroxysmal tachycardia. The patient died suddenly at 1:10 P.M. No necropsy was obtained.

Comment.—It is difficult to analyze this case other than to comment that a ventricular rate of 160 imposed upon a very bad heart was an intolerable load.

CASE 2.—P. F. (No. 34-732), a woman 76 years of age, was admitted on Nov. 11, 1943. She had a history of diabetes and hypertension since 1923. Electrocardiograms made on November 13 and November 19 revealed a pattern of anterior myocardial infarction (Fig. 2). Auricular premature beats were seen in the tracing of November 13 and two ventricular premature beats in the tracing of November 19. On November 21, the patient developed sudden right hemiplegia and a regular tachycardia of 180 per minute. After the tachycardia appeared, digitalis was given in doses of 3 grains every four hours for six doses and then grains 1½ twice daily. Following the sixth dose (total dose of 18 grains), on November 22, the electrocardiogram revealed supraventricular paroxysmal tachycardia. The tachycardia continued and digitalis was continued, grains 1½ daily. The patient died suddenly on Nov. 26, 1943. No necropsy was obtained.

Comment.—Supraventricular paroxysmal tachycardia developed coincident with hemiplegia probably due to cerebral embolism from an intracardiac thrombus. The load which the persistent tachycardia which lasted five days imposed upon a badly damaged heart was intolerable.

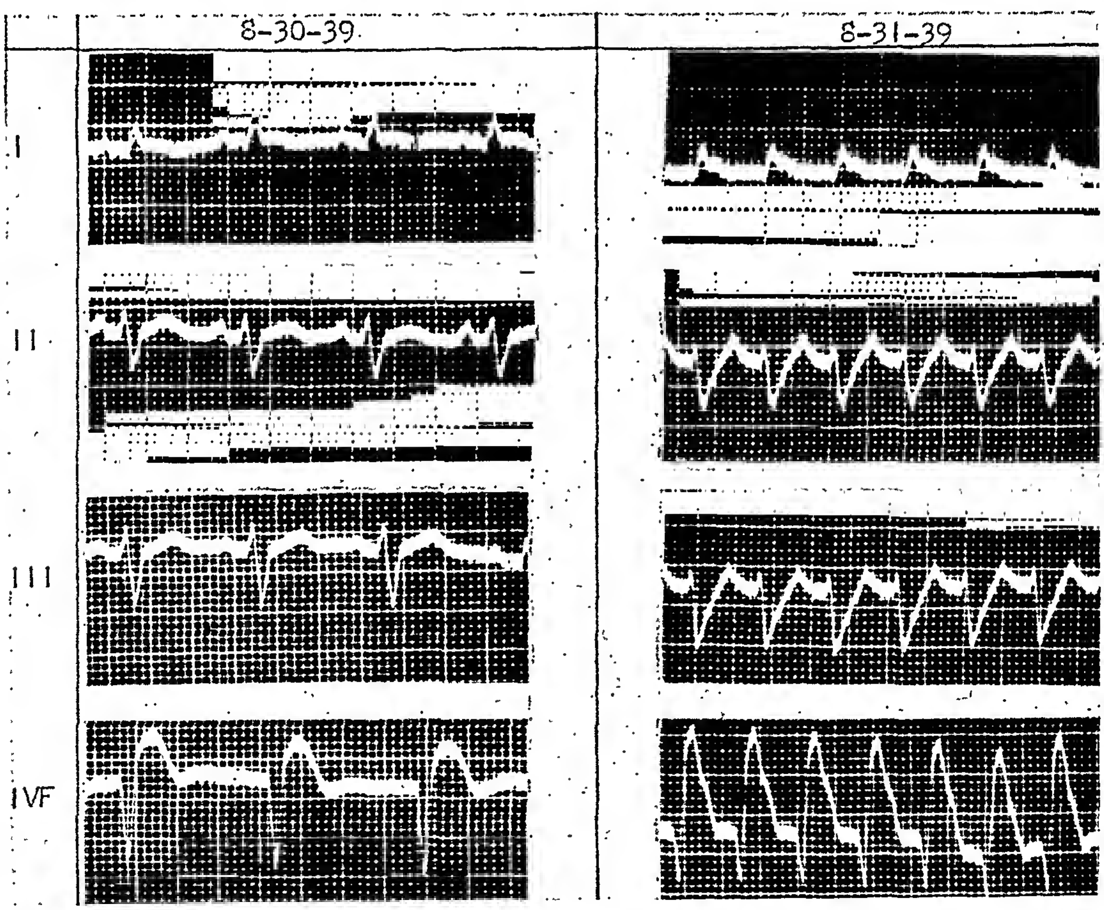

Fig. 3.—Case. 3. Aug. 30, 1939: Anterior myocardial infarction. Intraventricular conduction defect.
Aug. 31, 1939: Atrial paroxysmal tachycardia. Intraventricular conduction defect.

CASE 3.—P. F. (No. 609-955), a man 67 years of age, was admitted on Aug. 28, 1939. One week before, he had had knife-like, suffocating chest pain over the precordium radiating into the left side of the neck. He was dyspneic and apprehensive. A cold, clammy perspiration and a rapid, feeble pulse were present. The attack subsided in a few hours, but pain occurred daily and became continuous after the third day. On admission, because of pulmonary edema and distended cervical veins, he was given the powdered leaf of digitalis, grains 4½ every four hours for seven doses, and then grains 1½ daily. The patient received 33 grains in thirty-one hours. The next day he developed nausea and persistent vomiting. This was ascribed to overdigitalization. An electrocardiogram made on August 30 revealed a pattern of intraventricular conduction defect and anterior myocardial infarction (Fig. 3). On August 31, atrial paroxysmal tachycardia and intraventricular conduction defect were shown. Quinidine was then given in doses of 5 grains every four hours. The pulmonary edema increased, the tachycardia persisted, and the patient died at 12:50 A.M. on Aug. 31, 1939. No necropsy was obtained.

CASE 4.—P. F. (No. 608-060), a man 72 years of age, was admitted on May 8, 1938. Four days earlier he had developed sudden acute dyspnea and ankle swelling. Serial electrocardiograms made on May 9 and May 11 were considered consistent with anterior myocardial infarction (Fig. 4). He was discharged against advice on May 29, 1938.

He was readmitted on June 29, 1940. In the interim he had been dyspneic, needing two pillows in order to sleep, and for the past year, had had ankle edema. On the morning of June 29, he had had sudden substernal pain. He became orthopneic, cyanotic, and developed diffuse lung râles, left hydrothorax, and ankle edema. The liver, enlarged to the umbilicus, was tender and smooth. An electrocardiogram taken on July 1 showed the pattern of posterior myocardial infarction and intraventricular conduction defect with nodal rhythm. Digitalis was started on July 29 and a total of 24 grains was given. An electrocardiogram taken on July 2 showed supraventricular tachycardia. He died at 9:55 P.M. on July 2, 1940. A post-mortem examination revealed a recent posterior myocardial infarction and scars consistent with an old anterior lesion. The right coronary artery was occluded with a thrombus.

Comment.—Auriculoventricular nodal paroxysmal tachycardia developed following administration of 24 grains of digitalis in a man, 74 years of age, who had had a severe infarct two years after the initial attacks. He was digitalized because of right and left heart failure.

The patient and also the patient in Case 3 had bundle branch block, and the tachycardia in both patients, if seen without the previous tracings, could have been thought to be ventricular paroxysmal tachycardia. In both instances, large doses of digitalis were given and supraventricular tachycardia occurred the following day.

Auricular Paroxysmal Tachycardia in Association With Auricular Fibrillation.—The association of these two arrhythmias in heart disease other than acute myocardial infarction has been pointed out recently by Decherd and Herrmann[6,7] as not a rare occurrence. Auricular paroxysmal tachycardia is a rare complication of myocardial infarction, however, and its association with auricular fibrillation in this condition is extremely uncommon.

CASE 5.—P. F. (No. 541-863), a man 66 years of age, with no known previous cardiovascular disease, was admitted on April 22, 1940. An electrocardiogram taken on April 23 revealed the pattern of anterior myocardial infarction with auricular fibrillation and intraventricular block (Fig. 5). Digitalis was given in the following dosage: grains 28 of the powdered leaf in the first twenty-four hours and then grains 1½ daily. The next day, April 24, the electrocardiogram in the beginning of the tracing showed sinus tachycardia followed by a short run of auricular fibrillation, and the remainder represented auricular paroxysmal tachycardia. Quinidine was ordered in dosage of grains 3 four times daily. Despite the intraventricular block, the risk of the tachycardia seemed worse than that of the quinidine. The next day, April 25, sinus rhythm had returned. Digitalis, grains 1½ daily, was continued and quinidine, grains 3, was given after meals.

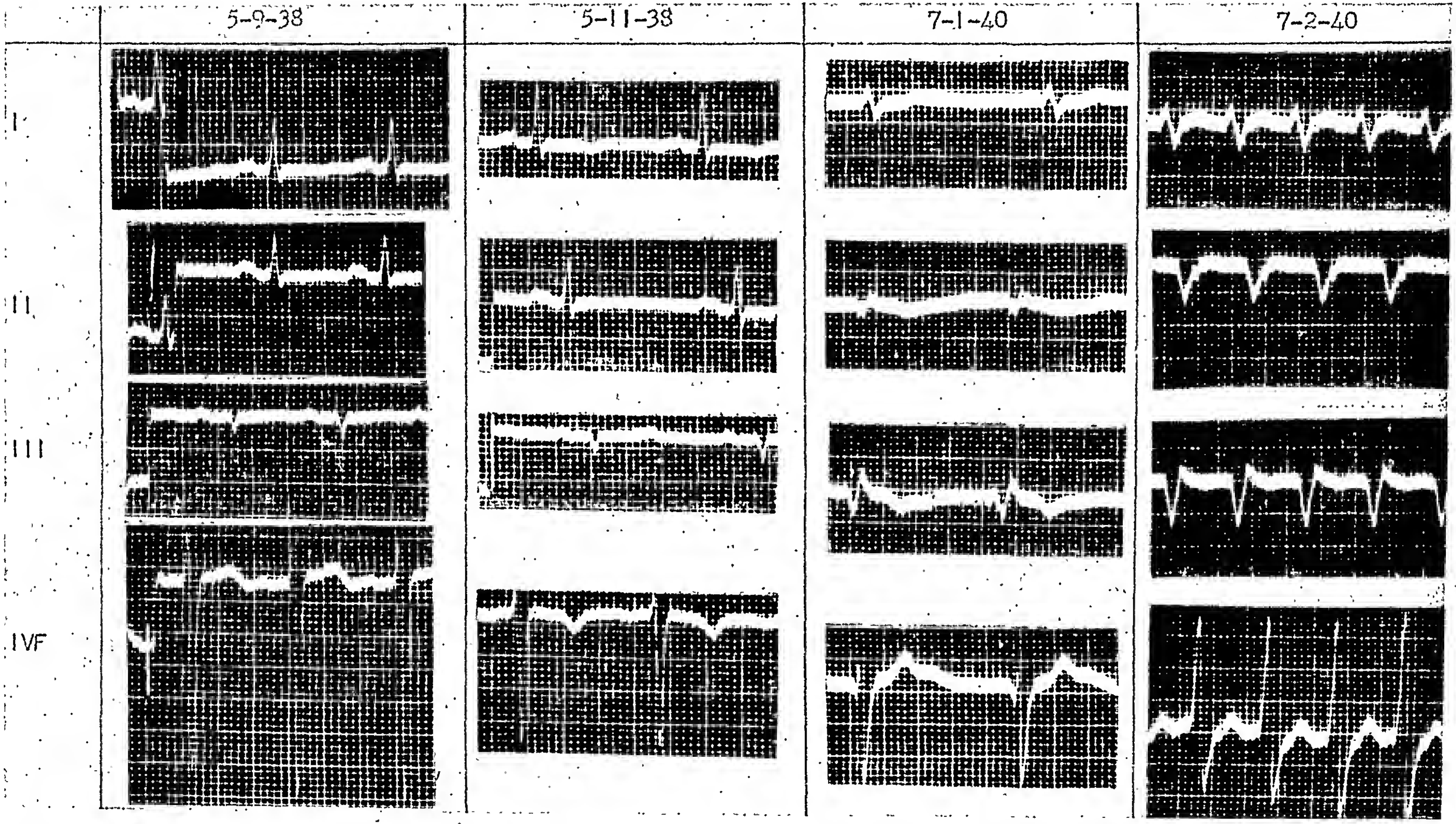

Fig. 4.—Case 4. May 9, 1938, and May 11, 1938: Anterior myocardial infarction.

July 1, 1940: Posterior myocardial infarction. Intraventricular conduction defect. Auriculoventricular nodal rhythm.
July 2, 1940: Supraventricular tachycardia. Auriculoventricular nodal origin. Rate 144.

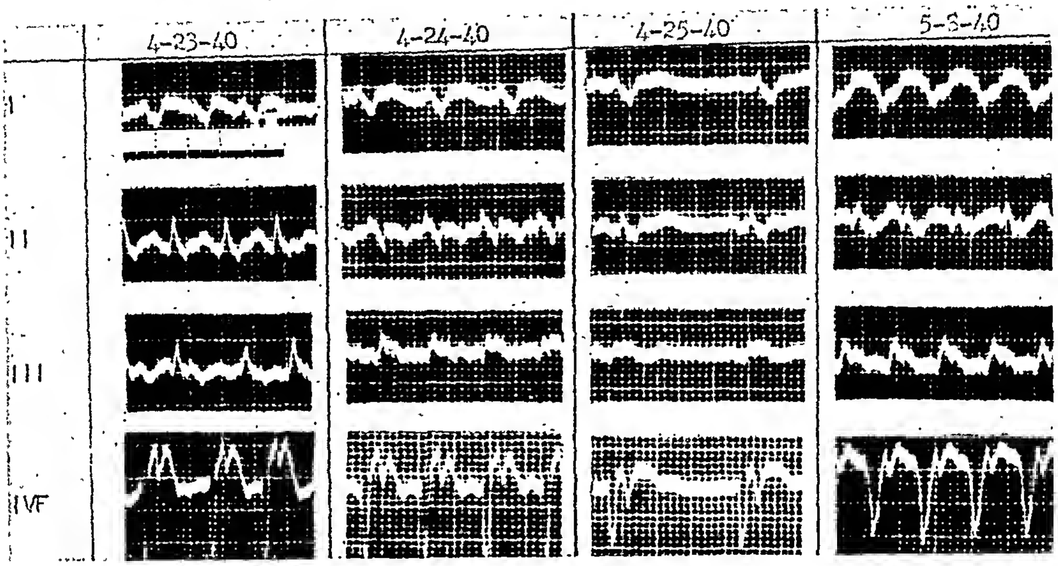

Fig 5.—Case 5. April 23, 1940: Auricular fibrillation. Intraventricular conduction defect. Anterior myocardial infarction.

April 24, 1940: Auricular paroxysmal tachycardia. Lead III isoelectric segment.
April 25, 1940: Sinus rhythm. Intraventricular conduction defect.
May 8, 1940: Auricular paroxysmal tachycardia. Lead III isoelectric segment.

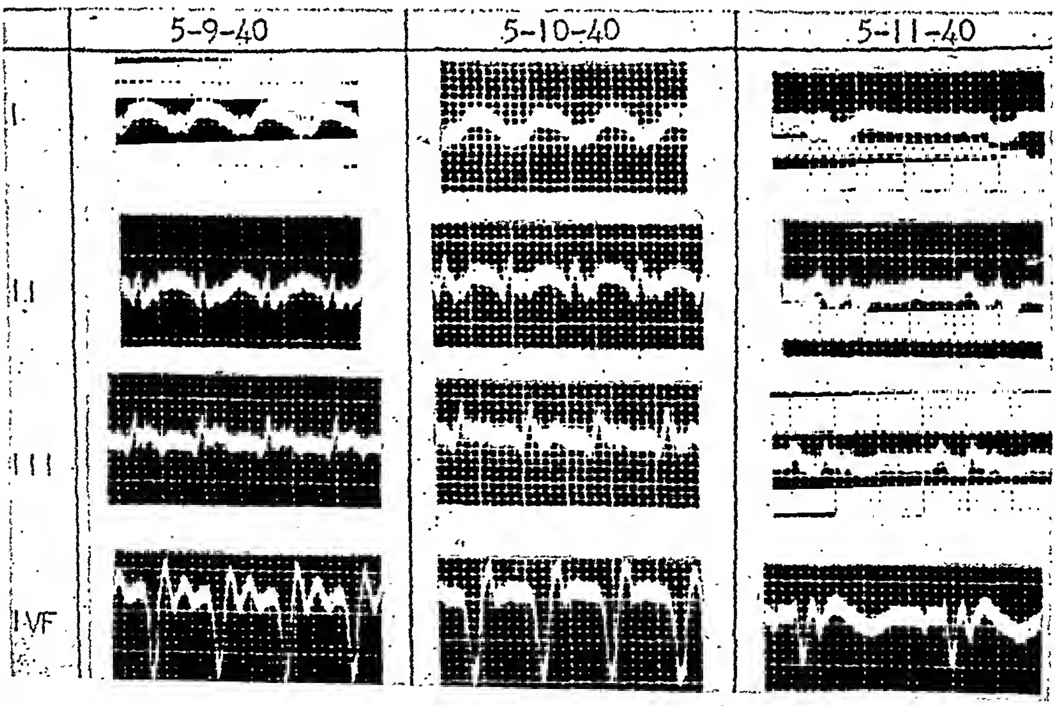

Fig. 6.—Case 5. May 9, 1940: Auricular paroxysmal tachycardia. Intraventricular conduction defect. Lead III isoelectric.

May 10, 1940: Auricular paroxysmal tachycardia.
May 11, 1940: Sinus rhythm. Intraventricular conduction defect.

On May 8 the arrhythmia was first diagnosed as auricular flutter with a ventricular rate of 190. A review of the tracing, however, indicates the arrhythmia to be auricular paroxysmal tachycardia at a little slower rate. Aside from the ventricular rate, which is rare for auricular flutter, there is a definite isoelectric segment present in Lead III. This has been emphasized by Decherd and Herrmann as the one dependable criterion for the differentiation of the two tachycardias in questionable cases. The patient's condition was so desperate, because of the continued tachycardia, that it was decided to give quinidine by vein. On May 9, 22 grains of quinidine dissolved in 400 c.c. of isotonic saline solution were administered. The tachycardia persisted and the electrocardiogram showed auricular paroxysmal tachycardia on May 10 (Fig. 6). The next day, May 11, the rhythm was normal but the patient had diffuse pulmonary edema, then developed pneumonia, and died two days later, May 13, 1940. Apparently heroic therapy in this case was useless, and death was ascribable to an uncontrolled ventricular rate of 200 per minute for four days.

Comment.—Although transitions from auricular fibrillation to auricular flutter are not uncommon in heart disease, transitions from auricular paroxysmal tachycardia to flutter or fibrillation are relatively uncommon. It apparently is a grave prognostic omen. Eight of the fourteen patients reported by Decherd and Herrmann died soon after they were observed. In only one was the diagnosis of myocardial infarction established.

DISCUSSION

Supraventricular paroxysmal tachycardia obviously is not an arrhythmia that is attributable to serious arteriosclerotic heart disease since it is found so rarely in myocardial infarction. It is true, however, that it occurred in the patients of our series with marked, long-standing heart damage. Probably all of these patients had had previous infarcts, and coronary atherosclerosis and ischemia were extreme. It is interesting and possibly significant that Rosenbaum and Levine found no instances of auricular paroxysmal tachycardia in their group of patients who presumably were suffering from their first attack. Master, Jaffe, and Dack[8] said that heart failure was present in all of their cases. It is apparent, therefore, that supraventricular tachycardia in relation to myocardial infarction is an arrhythmia which appears usually in those patients with extensive, long-existent heart damage.

Its appearance becomes of serious prognostic significance. Sinus tachycardia, which involves a ventricular rate only slightly over 100, is known to increase the mortality.[9,10] In a recent study of 572 patients at the Michael Reese Hospital, the mortality of the entire group was found to be 21.8 per cent. In the group with congestive failure, the mortality was 41.9 per cent. Mintz and Katz observed that "the combination of tachycardia and congestive failure is of graver prognostic significance than either alone." The greater load of a faster ventricular rate such as is produced by supraventricular tachycardia obviously should increase the mortality even more than sinus tachycardia, and it apparently does.

The gravity of supraventricular tachycardia should depend largely upon the degree of pre-existing damage and upon the duration of the tachycardia. Master and his co-workers found nine instances of paroxysmal tachycardia occurring in 300 patients with coronary artery thrombosis. All nine patients had heart failure and had an enlarged heart and hypertension. Of these, five were idenfied as supraventricular in origin by electrocardiographic tracings. One was

ventricular in origin. The other three patients had no tracings taken. Only two of the nine patients died. The tachycardia occurred in a group which enjoyed one of the lowest reported mortality rates (8 per cent). Furthermore, the duration of the tachycardia was less than twenty-four hours. The immediate mortality of the group of patients with myocardial infarction in which our five instances occurred was 51 per cent. In none of our patients did the tachycardia disappear. Three died within twenty-four hours after the onset of the tachycardia and two after its persistence for four and five days.

The question of the etiology of the arrhythmia is interesting. Decherd and Herrmann believe that digitalis in excessive amounts may precipitate auricular paroxysmal tachycardia. In three of our five patients, the arrhythmia followed the administration of large amounts of the drug within a short time. In Case 3 the patient received 33 grains within thirty-one hours and was obviously overdigitalized, as evidenced by persistent vomiting. In Case 4, 24 grains were given in twenty-four hours prior to the development of the arrhythmia. In Case 5, the patient received 28 grains the day preceding the onset of the arrhythmia. That the tachycardia in three of the five patients should follow large doses of digitalis would appear to be more than coincidence. This would tend to favor the belief of Decherd and Herrmann. They studied forty patients with auricular paroxysmal tachycardia and auriculoventricular block and found that twenty-three of these had received an obvious overdosage of digitalis.

In two of our patients digitalis was administered because of marked right and left ventricular failure. In the others, the presence of auricular fibrillation was the indication. Whether or not digitalis was the precipitating factor can only be conjectured. It does suggest the wisdom of not digitalizing too rapidly patients with myocardial infarction.

SUMMARY

Supraventricular tachycardia appeared in five instances only in 1,247 patients with myocardial infarction observed at the Los Angeles County Hospital. The mortality was 100 per cent.

It is a rare arrhythmia to be associated with myocardial infarction. It was usually associated with grave, long-standing heart damage. Its seriousness depends upon the degree of heart damage and the persistence of the tachycardia. It apparently followed overdigitalization in some instances. Prognostically, the appearance of supraventricular tachycardia in myocardial infarction would seem to be of grave portent.

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Clinical Reports

SCOLIOSIS AND CARDIAC FAILURE

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CARDIAC or pulmonocardiac failure which results from severe deformity of the chest is not rare. The following case is reported because it illustrates many of the common clinical and pathological features of this condition.

CASE REPORT

A 19-year-old unmarried white girl, a patient of Dr. J. W. Martin, entered the hospital with the complaint of shortness of breath for three weeks. In 1929, at the age of 2½ years, the patient had acute anterior poliomyelitis. When first seen at the University Hospitals, at the age of 4, she was of normal size and fairly well nourished. There was weakness or paralysis of numerous muscles of the extremities and trunk. Without support, she was unable to sit up or to walk. Thoracic breathing was somewhat weaker than normal, but the respiratory excursion was equal bilaterally. The heart and lungs were normal. Bed rest, physiotherapy, and nightly splinting of the legs and feet resulted in no improvement at the end of one year. Numerous surgical procedures performed on the extremities during the years 1933 to 1938 resulted in the patient's being able to use crutches and to walk fairly well. She did not tolerate operations well, however, usually developing acidosis, slight fever, and tachycardia for several days postoperatively.

A left dorsal-right lumbar scoliosis was first noted in 1932. It progressed in severity until 1941. Celluloid jackets worn since 1933 had become impracticable by 1938 because of marked deformity of spine and chest. On examination in that year, the patient was poorly developed and considerably underweight, but no abnormalities of the heart or lungs were detected.

Beginning in 1943, the patient suffered frequent colds and easy fatigue and developed tachycardia and progressive dyspnea and orthopnea. In February, 1946, fourteen years after the onset of scoliosis and three weeks before death, her shortness of breath and palpitation increased greatly in severity and she had frequent epistaxis. Four days before her final admission to the hospital, her physician noted cyanosis, râles at the bases of the lungs, and accentuation of the second pulmonic sound. He began digitalization. On admission to the hospital she was deeply cyanotic, dyspneic, and orthopneic. The temperature was 38°C., the pulse rate 150, the respiratory rate 40, and the blood pressure 115/75. Basal râles and an apical systolic murmur were heard. There was minimal pitting edema of the ankles. She was placed in an oxygen tent and 20,000 units of penicillin, ¾ grain of sodium phenobarbital, and ⅛ grain of morphine were administered. Her condition rapidly grew worse and she died one hour and forty-five minutes after admission.

Autopsy (No. 9510).—The body was that of a poorly developed, moderately well-nourished young woman of immature appearance. The body weight was 28 kg. (61.6 pounds), the length 120 cm. (4 feet). Lips and nail beds were cyanotic and cervical veins were distended. The thorax

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was narrow and bulged forward on the right. On the left, rotation and angulation of the ribs displaced the medial margin of the scapula and produced a marked posterior protrusion. The trunk was greatly shortened, occupying only about one-fourth of the body length. The extremities showed varying degrees of muscular atrophy and the scars of numerous surgical operations.

Fig. 1.—Roentgenogram of the spine, made at age of 8 years, four years after onset of scoliosis. The greatest degree of scoliosis is in the thoracic spine. Further progress of scoliosis occurred during the next five years.

All thoracic and lumbar vertebrae were involved in a U-shaped curve to the left, with its apex at the eighth and ninth thoracic vertebrae. The opposing surfaces of its arms were 16 cm. apart. The associated rotation of vertebrae to the left amounted to nearly 90° at the apex of the curve and the ribs were correspondingly deformed and displaced. The space between the apex of the spinal curve and the left ribs admitted only the tips of the fingers. A small portion of the left lung lay within this crevice. The remainder was anterior to the spine and partly overlaid it. The trachea was in the midline. The heart lay directly beneath the sternum and was rotated

about 10° to the left. The descending aorta followed the curve of the spine. The abdominal viscera occupied approximately normal positions.

The heart weighed 250 grams. The right atrium and ventricle were considerably dilated, the former to approximately twice the normal volume. The right ventricle was 6.0 mm. thick, the left ventricle 14 millimeters. Columnae carneae were enlarged and flattened, particularly in the right ventricle. Tricuspid, mitral, and aortic valves showed slight thickening and opacity without deformity. Coronary arteries, aorta, and pulmonary artery were normal.

The right lung weighed 370 grams, the left 350 grams. Both were small, the left particularly, and had the general appearance and texture of infantile rather than adult lungs. There was general moderate diminution of crepitancy, notably in the lower lobe of the left lung. Scattered foci of increased density up to 3.0 cm. in diameter were reddish purple, granular, and slightly elevated on section. Tissue elsewhere was dark red and moist. Alveoli were inconspicuous.

The liver weighed 820 grams. The central zones of its lobules were large and dark red. The spleen weighed 90 grams and had a wet, soft, purplish red cut surface. The kidneys weighed 100 grams each and showed prominence of small blood vessels. Other organs, including the brain, were grossly normal.

Microscopic Description of Lungs: The pleurae showed occasional small deposits of black pigment. In the parenchyma, particularly of the lower lobe of the left lung, there were many foci in which the lumina of alveoli were reduced and sometimes indistinguishable. Elsewhere, alveoli were sometimes distinctly dilated and their septa were shortened. In all sections, alveoli contained red blood cells, sometimes in large, dense foci, and numerous large mononuclear cells with faintly stained cytoplasm and vesicular oval nuclei containing finely granular chromatin. Occasional polymorphonuclear leucocytes were seen in alveoli, but they seldom formed appreciable aggregates. The bronchi contained similar cells. Blood vessels were dilated. Their walls were normal. Slight bronchiolar dilatation was an occasional observation.

Principal pathological diagnoses were cardiac hypertrophy and dilatation, especially manifest in right ventricle and atrium (cor pulmonale), moderate hypoplasia of the lungs, especially of the left lung, focal atelectasis of the lungs, focal chronic pulmonary emphysema, slight bronchopneumonia, atrophy of the anterior columns of the spinal cord consistent with healed poliomyelitis, scoliosis of the thoracic and lumbar vertebrae, and atrophy of skeletal muscle of the trunk and extremities.

COMMENT

The incidence of some degree of scoliosis following acute anterior poliomyelitis has been variously reported at 5 to 30 per cent.[1,2] According to Kleinberg,[1] in the majority of children scoliosis begins within five years after the acute illness and may progress throughout the remainder of the growth period. Maximum deformity has usually developed by the time the patient has reached young adulthood. The shortened life expectancy of persons in whom severe thoracic deformities have developed early in life has been long recognized.[3] Exceptions occur,[4] of course, but in seventy-nine cases collected by Chapman, Dill, and Graybiel,[5] the average age at death was 30 years. These authors, whose paper forms the basis for part of the following discussion, believe that pulmonocardiac failure is of common occurrence in severely deformed patients and is the most frequent cause of death.

The earliest and outstanding cardiorespiratory symptoms in severe deformity of the chest are dyspnea and tachycardia. These symptoms may persist for years, progressing slowly. Cough and epistaxis are frequent. Susceptibility to respiratory infections is increased and the effects of such infections are usually pronounced. A distinct intolerance to morphine has been frequently noted, administration of the drug having been followed by fatal respiratory depression

in numerous instances. The onset of severe dyspnea on slight exertion or attacks of paroxysmal dyspnea, asthma, great weakness, or fainting mark the beginning of pulmonocardiac failure. Death usually follows soon.

On physical examination the patients are small, frail, and dyspneic. Tachycardia is always present and the second pulmonic sound is frequently accentuated. Clubbing of the fingers does not occur. Cyanosis and edema are late signs, and the latter may never appear.

At autopsy, the lungs are small and are often described as resembling the lungs of children. Their small size has sometimes been attributed to hypoplasia; sometimes, with less reason, to atrophy. Focal pulmonary emphysema and atelectasis are often present and pneumonia of varying extent is found in the majority of cases. The most common cardiac abnormalities are hypertrophy and dilatation almost confined to the right ventricle. A shift in the position of heart or great vessels is an inconstant observation, seldom striking, and of doubtful significance. Edema and passive hyperemia of the viscera are frequent, but not often of great degree.

How deformity of the chest results in pulmonocardiac failure is not fully understood, but there is much to indicate that reduction of thoracic volume and faulty respiratory mechanics are chiefly responsible. The size of the lungs is limited by the small thoracic volume, and their effective size is further reduced by atelectasis and emphysema. To this static handicap is added the limitation of respiratory movement resulting from skeletal deformity and from weakness and poor mechanical effectiveness of the muscles of respiration.

Deficiencies in thoracic volume and respiratory excursion may have numerous secondary effects. The smaller size of the lungs reduces absolutely both the amount of air and blood which they can contain and the area of the interface where exchange of gases between air and blood can occur. Diminished respiratory excursion limits the normal inspiratory increase in the capacity of the lungs for air and blood and the normal increase in area of the interface. The increased breathing effort exerted in overcoming mechanical handicaps and maintaining gaseous exchange accounts for the characteristic dyspnea of severely scoliotic patients.

As has been indicated, two factors tend to reduce vascular capacity: (1) absolute reduction in number and size of vessels and (2) curtailment by diminished pulmonary expansion of the expansion of blood vessels which normally occurs in inspiration.[6,7] Since cardiac output is not reduced in the majority of scoliotic patients in whom it has been studied,[5] the effect of reduced vascular capacity is to increase pulmonary arterial resistance.* There is evidence, also, that in certain chronic pulmonary disorders, including kyphoscoliosis, the associated increase in ventilatory effort is accompanied by a greater than normal inspiratory increase in right ventricular output; an increase dependent on increase in negative intra-

*Since this report was submitted for publication, attention has been drawn to the possibility that in kyphoscoliosis, oxygen lack resulting from poor ventilation of the lungs may induce local constriction of pulmonary arterioles and precapillaries with resultant increase in pulmonary arterial resistance. (McMicheal, J.: Heart Failure of Pulmonary Origin, Edinburgh M. J. **55**:65, 1948.)

The existence of pulmonary arterial hypertension in kyphoscoliosis has been demonstrated. (Medical Grand Rounds, American Practitioner **2**:764, 1948.)

thoracic pressure.[8,9,10] To the extent that the expansibility of the lungs may be reduced in these disorders, as by pulmonary fibrosis, it is likely that change in intrathoracic pressure is not accompanied by a normal proportionate change in pulmonary volume. It may be, therefore, that during each inspiration the discrepancy between right ventricular output and pulmonary vascular capacity is widened. Moreover, a pumping action on the lesser circulation, which Macklin[11] believes is exerted by stromal pull on pulmonary vessels during inspiration and by elastic recoil of the lungs during expiration, would presumably be reduced as a result of diminished respiratory excursion in thoracic deformity. If the view is correct that the action of this "pulmonary accessory heart" is normally beneficial,[7] it can be argued that a reduction of such pumping action is deleterious to cardiocirculatory function. It is recognized, however, that the concept of a pulmonary accessory heart, though plausible, is unproved.

Once pulmonocardiac failure begins, available therapeutic measures offer little hope of recovery. Rest, digitalis, and diuretics are largely ineffective, and morphine is often contraindicated. The goal of medical care in deformed patients is therefore the prevention of pulmonocardiac failure. In its attainment, general hygienic measures and the avoidance of respiratory infections are the principal considerations.[5]

Prevention of deformity itself is, of course, the primary objective. Such prevention requires first the recognition of the likelihood of scoliosis following acute anterior poliomyelitis and of the likelihood of its progression to severe deformity. Second, it requires that measures undertaken after the acute illness be directed no less intensively at preventing scoliosis than at preventing other musculoskeletal defects. The well-known difficulty of correcting or even halting the progression of paralytic scoliosis emphasizes this point. Finally, if scoliosis develops and progresses despite preventive measures, efforts at correction of the deformity, probably including spinal fusion, support, and muscle training, must be well planned, prompt, and unremitting.

SUMMARY

A typical case of cardiac failure in a patient with paralytic scoliosis is reported.

Important effects of thoracic deformity are to limit pulmonary ventilation, to impede the pulmonary circulation, and to alter respiratory fluctuations in blood flow. Increased ventilatory effort, tachycardia, and right ventricular dilatation and hypertrophy are thereby induced. If these responses can be considered compensatory, they are inadequate to permit normal development and activity and they ultimately fail completely.

Treatment is largely preventive, and begins with prevention or correction of the thoracic deformity itself.

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CORONARY ARTERIOVENOUS FISTULA

Case Report

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THE following case report describes a congenital cardiovascular anomaly unique in our experience and, we believe, not hitherto suggested as a possible diagnosis during life. A similar anomaly, discovered incidentally at autopsy, has been the subject of a report by Halpert.[1]

R. P., a boy of 9 years, was admitted to the Surgical Service of the Massachusetts General Hospital on June 24, 1947, for study of a continuous murmur heard maximally in the right parasternal region. His mother stated that she had been in good health during her pregnancy and that the child was delivered uneventfully. (The record of the hospital where the child was delivered does not mention any cardiovascular abnormalities.) He developed normally during infancy but at the age of 2 years was admitted for a few days to another hospital because of a transient right hemiplegia of unknown cause. The hospital record of this illness stated that a loud apical systolic murmur was present. When 5 years old, the boy became ill with scarlet fever, and his family physician also noted the presence of a heart murmur and referred him to the Massachusetts General Hospital for evaluation of his cardiac status. There had been no joint pains or other symptoms suggestive of rheumatic fever.

When first seen in the Out Patient Department on May 15, 1943, the child was entirely symptom free and appeared to be in good health. The only abnormalities described were enlargement of the tonsils, questionable cardiac enlargement, and the presence of a loud apical systolic murmur followed by a third sound and a short diastolic rumble. An electrocardiogram was normal. Chest x-ray films were not remarkable except for slight cardiac enlargement (Fig. 1). Over the course of the next four months other examiners noted the disappearance of the diastolic rumble, and it was observed that the systolic murmur described as "apical" was actually loudest along the lower right sternal border and in that area was part of a definite continuous murmur.

During the subsequent three and one-half years the patient remained in good general health without any complaints suggestive of an impaired cardiac reserve, and with no change in the physical findings. He underwent a tonsillectomy in 1945 and a circumcision in 1946 without difficulty.

In view of the continuous character of the murmur, the diagnosis was made of an arteriovenous fistula, the exact location of which was in doubt (the chest wall, right lung, and internal mammary and coronary vessels were all mentioned as possibilities). If the patient had also had rheumatic fever with myocarditis following scarlet fever at the age of 5 years as an explanation for the transient apical diastolic rumble, there was no longer any clear evidence of rheumatic heart disease. Since it was believed possible that the continued existence of the arteriovenous fistula might result in significant myocardial strain over the course of time, and because it also appeared possible that this fistula might be excised, operation was advised.

On admission to the Surgical Service on June 24, 1947, he was seen to be a well-developed and well-nourished young boy, who was not dyspneic on effort and who showed no cyanosis.

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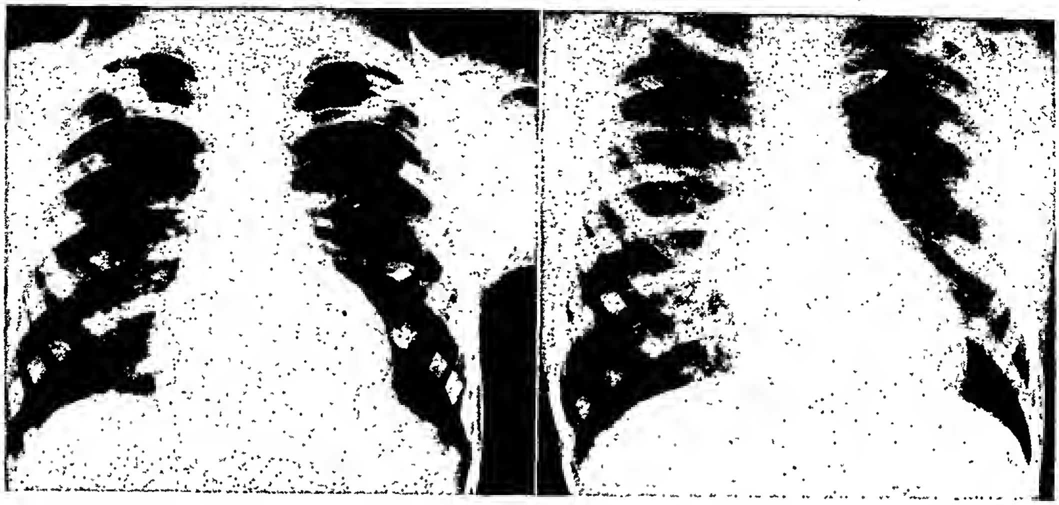

Fig. 1.—Chest x-ray films showing slight cardiac enlargement. *A*, May 18, 1943; *B*, May 8, 1947.

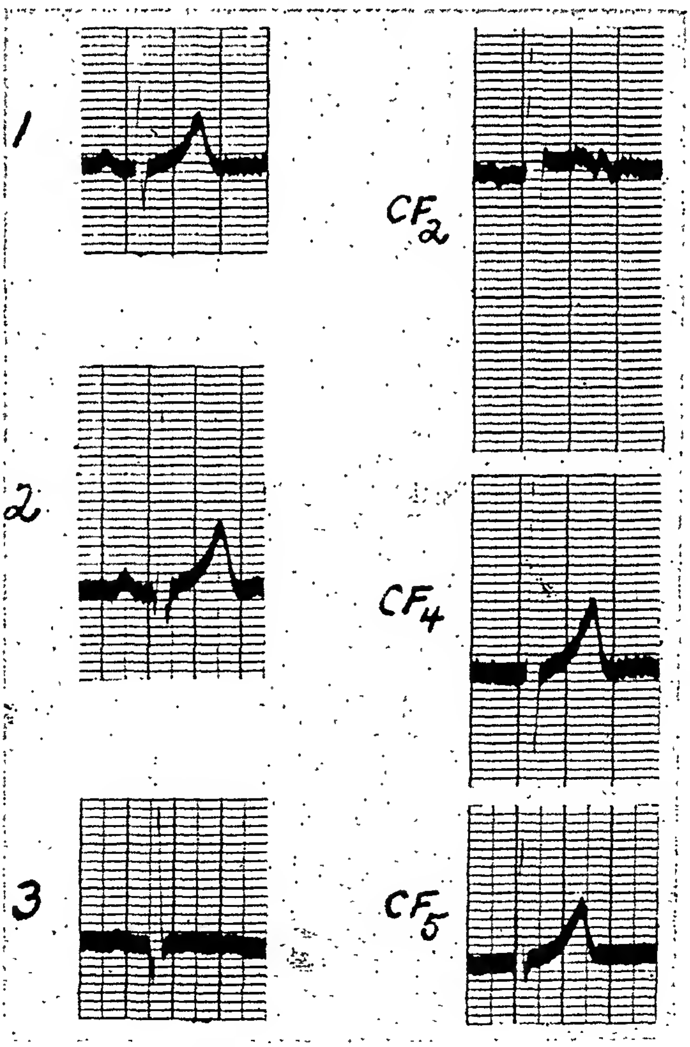

Fig. 2.—Electrocardiogram taken May 16, 1947, showing normal complexes throughout.

The pulse rate was 72 and the blood pressure was 110/75. The pupils reacted normally to light and accommodation, the throat was clean, and the carotid pulsations were equal bilaterally. The neck veins were not remarkable. The thoracic cage was normally proportioned, and the lung fields were resonant and clear. Examination of the heart showed the maximal apex impulse to be at the left midclavicular line in the fifth intercostal space. The second sound in the pulmonic area was louder than the second aortic sound. In the fourth right intercostal space adjacent to the sternal border there was heard a continuous murmur, the systolic component of which was of Grade 3 intensity. The systolic phase of this murmur was well heard at the cardiac apex and at the base of the heart but was not transmitted to the lung bases or down the spine. No thrill was present, and no other murmurs were heard. The liver and spleen were not palpable, there was no edema, and the peripheral pulsations were normal. There was no clubbing of the fingers or toes.

Routine blood studies were not remarkable, and a urine specimen was negative. The blood Hinton reaction was negative. Chest x-ray films taken one month previously (Fig. 1) were reviewed and were considered to show normal lung fields and a heart shadow which was at the upper limits of normal in size or possibly slightly enlarged. The shape of the heart was not characteristic of any specific pathological condition. An electrocardiogram (Fig. 2) was also within normal limits.

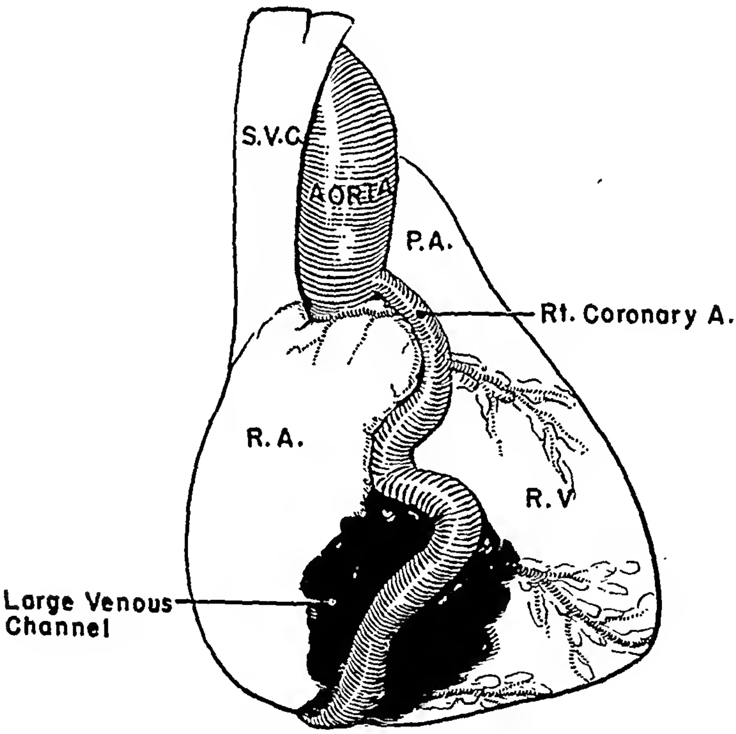

Fig. 3.—Drawing (based on a sketch made at operation) showing the relative size and position of the right coronary artery and the dilated venous channel.

On June 25, 1947, an exploratory thoracotomy was performed (by R. H. S.). The operative note reads as follows:

A long oblique incision was made across the right chest which was opened through the sixth intercostal space. This gave an excellent exposure. The lung was not adherent. It was found on palpation and inspection to be completely normal. Inspection of the anterior thoracic wall showed no evidence of a fistula in the internal mammary vessels, but it soon became apparent that there was an abnormal coronary artery which could be seen through the thin pericardial layer. The pericardium was then incised and retracted so as to give a good exposure of the

right portion of the heart. The right coronary artery was enormously dilated and tortuous (Fig. 3). At its origin from the ascending portion of the aorta it was felt to be about 6.0 mm. in diameter. In its widest portion as it descended along the auriculoventricular groove it was about 1.0 cm. in diameter and very thick walled. The vessel continued in its usual course around posteriorly where it appeared to meet with a large venous channel in the wall of the auricle. This was undoubtedly the coronary vein as it emptied into the coronary sinus. It seemed unlikely that anything could be accomplished surgically in this case by ligation of this vessel, excision, or otherwise, without serious damage to the circulation to the heart muscle and it seemed unlikely also that this defect was causing him any serious difficulty. It was therefore decided that nothing should be done. The incision in the pericardium was closed with fine silk sutures and the lung was expanded. The chest wall was then closed, using pericostal sutures of catgut, with silk in the remaining layers, the postoperative diagnosis being arteriovenous fistula between the right coronary artery and right coronary vein.

It was observed during the procedure that a marked thrill could be felt by placing the gloved finger over this group of abnormal vessels.

The patient recovered uneventfully from the operation and was discharged from the hospital on July 7, 1947. When last seen on Dec. 9, 1947, he was in excellent health, attending school, and leading a normal life. The physical findings were unchanged.

COMMENT

It would be unwise to try to predict too accurately the outcome in this case. Halpert's[1] patient, also male, died at the age of 54 years from carcinoma of the stomach without obvious symptoms of heart disease. (Indeed, no evidences of cardiovascular abnormality were detected during life.) At autopsy the heart was found to be hypertrophied, weighing 500 grams; a large, tortuous right coronary artery, 1.5 to 2.0 cm. in diameter, was present which emptied into the coronary sinus via an anastomotic loop. This loop also was markedly tortuous and on microscopic study its structure was seen to be intermediate between artery and vein. The similarity between the findings in this case and in ours is striking. We believe that the importance of the abnormal coronary arteriovenous communication in our patient probably lies not so much in its effect on the blood supply to the myocardium (doubtless an adequate collateral circulation from the left coronary artery is present) as in its useless diversion of a portion of the left ventricular output back into the right auricle, and in the fact that it is a potential locus for baterial endarteritis. However, since congenital arteriovenous fistulas of this caliber are as a rule remarkably well tolerated, we do not anticipate difficulty for many years.

We have encouraged this boy to lead a normal life, have advised semiannual examinations to evaluate his cardiac status, and have recommended the administration of penicillin prior to any dental extraction.

SUMMARY

A 9-year-old boy was operated upon to ascertain the origin of a continuous murmur heard maximally over the lower right sternal border. At operation an arteriovenous fistula connecting the right coronary artery and vein was discovered.

ADDENDUM

Dr. Robert E. Gross of the Children's Hospital, Boston, has kindly permitted us to include the following note on a patient on whom he has operated. A 16-year-old boy was admitted to the Children's Hospital in January, 1947, with a history of known heart disease since infancy. A diagnosis of patent ductus arteriosus complicated by streptococcal bacterial endarteritis had been made six weeks previously and the patient successfully treated with penicillin. On admission, a harsh continuous murmur associated with a thrill was present, maximal over the third and fourth intercostal spaces along the left sternal border. An exploratory operation was performed by Dr. Gross on Jan. 27, 1947, at which time an abnormal area characterized by bulging and thinning of the myocardium was found in the lateral wall of the left ventricle, located 2.0 to 3.0 cm. below and in front of the tip of the left auricle, about 3.5 cm. in diameter and associated with a thrill. The identity of any major vessels feeding into this region was not ascertained. No further surgery was undertaken, and the patient recovered uneventfully. The postoperative diagnosis was arteriovenous aneurysm, probably of the coronary system.

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VAGOVAGAL SYNCOPE: REPORT OF A CASE APPARENTLY INDUCED BY DIGITALIZATION

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Descriptions of vertiginous, syncopal, and convulsive attacks associated with a slow pulse have been described by Gerbezius (1719), Morgagni (1761), Adams (1826), Stokes (1846), and others. These attacks have become known as the Adams-Stokes syndrome, and a number of mechanisms for their production have been described. Many of these mechanisms are associated with low heart rates, all are associated with lowered or absent peripheral pulse, and all produce vertigo, syncope, or convulsions by reduction of blood flow through the brain.

Attempts at more exacting definition of the syndrome, by the inclusion of criteria not obtainable from history or clinical examination, have led to confusion in the use of the term. One commonly employed definition limits its use to seizures wherein atrioventricular block with prolonged ventricular diastole is present[1]; another, to heart block with ventricular standstill, tachycardia, fibrillation, or a combination of these.[2] Both definitions necessitate the use of infrequently available equipment at the time of the attack, inasmuch as the changes may be transient and present only at that time. Both eliminate those disturbances of cardiac rhythm, other than atrioventricular block, which may be associated with a slow or absent peripheral pulse. We fail to see the usefulness of such technical limitations (often impracticable of application because of the transient nature and unpredictable occurrence of the seizures) in a syndrome whose chief usefulness appears to be a simple, ever ready method of broadly differentiating the vertiginous, syncopal, or convulsive seizures of cardiac origin from those of metabolic, cerebral, or other origin. The definition first stated allows inclusion of the cases reported by Gerbezius, Adams, and Stokes, where the mechanism of the slow pulse was not graphically recorded and proved, those of Morgagni, where one case is somewhat suggestive of a reflex origin of the syndrome, as well as inclusion of the numerous cases reported where the Adams-Stokes episodes occurred before permanent heart block was present and failed to occur thereafter. To be retained in medical literature as a syndrome, the term must have a descriptive clinical significance and should include all the cardiac mechanisms producing a slow or imperceptible pulse with syncope.

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The mechanisms which might be included under this syndrome are: (1) paroxysmal auricular standstill with ventricular arrest; (2) paroxysmal and intermittent atrioventricular block with ventricular arrest; (3) permanent complete atrioventricular block associated with intermittent alteration of the sensitivity of the idioventricular pacemaker, with temporary alteration of the vascular tone, or with an increased metabolic demand not met by an increase in heart rate or stroke output; and (4) paroxysms of rapid ventricular beating (ventricular tachycardia, flutter, or fibrillation) with inaudible heart sounds and absent peripheral pulse.

The etiological factors described as responsible for producing these mechanisms include: (1) reflex mechanisms of carotid sinus-vagal, vagovagal, vasovagal, and central vagal types; (2) toxic or infectious lesions with reversible damage of the conduction system due to diphtheria, the rheumatic state, syphilis, trichiniasis, quinidine, digitalis, and strophanthus; (3) temporary anoxia of the conduction system seen in certain forms of rapid heart action, coronary sclerosis, myocardial infarction, and anoxia from obstructed airway, altitude, or oxygen-poor atmosphere; (4) permanent destruction of the conduction system about the auriculoventricular node from abscess, granuloma, neoplasm necrosis, or scarring; and (5) congenital defect of the conduction system.

In the neurogenic group, those of vagovagal origin apparently are infrequent, and especially infrequent are those of vagovagal origin in which the hyperactive reflex is associated with a diverticulum of the esophagus.

Weiss and Ferris[3] in 1934 described the first case of which we are aware of transient complete heart block in association with an esophageal diverticulum. Their patient was a 64-year-old white man without evidence of organic heart disease, who was studied after he was admitted to the hospital because of attempted suicide. For ten years he had suffered from intermittent fainting attacks induced by swallowing. Barium esophogram revealed an anterior "hooked" traction diverticulum at the junction of the middle and lower one-third of the esophagus, associated with dilatation of the lower one-third. Electrocardiographic studies were not obtained during the syncopal attacks, but the heart rate was found to be slow and irregular. These authors were able to reproduce the attacks by inflating a rubber balloon at the level of the diverticulum. Electrocardiograms recorded during balloon inflation revealed atrioventricular dissociation with a slow, irregular ventricular rhythm. Adrenalin and ephedrine prevented the syncope by means of the ready development of an idioventricular rhythm of approximately normal rate. Atropine abolished the syncope by preventing the atrioventricular block.

We have observed a patient who is an example of vagovagal syndrome secondary to an esophageal diverticulum. There was associated a vagal type of carotid sinus sensitivity. The patient is of interest because of the infrequency of reported cases of this type and because of observations concerning the mechanism of symptom production.

CASE REPORT

A 67-year-old white man presented himself on Dec. 10, 1941, at the Milwaukee County Hospital Out-Patient Clinic, complaining of choking, vomiting, fullness beneath the xiphoid process, dizziness, and fainting on eating or swallowing. These symptoms had been present for a single day. He had been receiving digitalis since April, 1941, because of breathlessness on exertion, which appeared to be due principally to chronic bronchitis and emphysema. Sipping water, precordial percussion, and pressure over the right carotid sinus produced asystole together with weakness, vertigo, syncope, and occasional epileptiform twitchings. Pallor and hypotension accompanied these episodes.

Electrocardiograms obtained at that time (Fig. 1,*A*) showed depression of the RS-T segment and flattening of the *T* wave suggestive of a digitalis effect. Tracings obtained under the test conditions named revealed the development of incomplete and complete atrioventricular block with a slow, irregular ventricular rhythm (Fig. 1,*B* and *C*). An esophogram revealed an "anterior diverticulum at the junction of the middle and distal one-third with dilatation of the distal one-third of the esophagus apparently due to obstruction at or near the cardia."

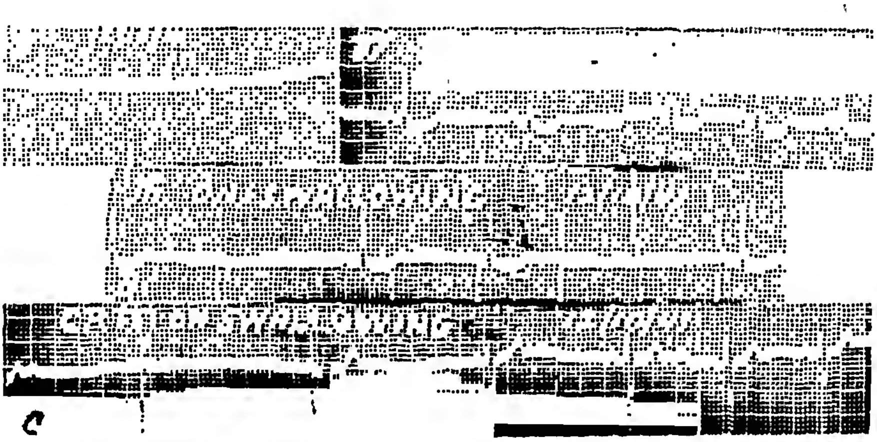

Fig. 1.—Electrocardiogram taken Dec. 10, 1941, at the time of spontaneous syncopal attacks produced by swallowing. Esophagram at this time revealed dilatation of the distal one-third due to obstruction at or near the cardia.

A, Leads I, II, and III. Note the downward convexity of the S-T segments and low amplitude of the T, compatible with digitalis effect.

B, Lead III, on swallowing, showing the development of low-grade atrioventricular block.

C, Lead CR_3, on swallowing, showing the development of low-grade atrioventricular block.

The symptoms cleared after the patient was given atropine, although carotid sinus stimulation continued to produce vertigo with insufficient cardiac slowing to cause syncope. Since 1941, he has experienced only one brief recurrence of symptoms which were reported to have been rapidly relieved by atropine followed by esophageal dilatation. He has continued to take digitalis constantly throughout the five-year period.

CLINICAL OBSERVATIONS

In November, 1946, a series of observations was begun on this patient in order to study the mechanism of production of the Adams-Stokes attacks. These observations are summarized in the following.

Observations From the History.—The syncopal attacks which appeared during swallowing occurred only when there was esophageal dilatation, apparently secondary to cardiospasm.

These attacks were associated with sinus bradycardia and incomplete and complete atrioventricular block with slow and irregular ventricular rhythm. This accounted for the pallor and moderate-to-profound hypotension, and when the attacks were prolonged, they produced cerebral anoxia of sufficient degree to cause syncope and convulsive twitchings.

There was hypersensitivity of the right carotid sinus of sufficient degree to produce syncope only during episodes of esophageal dilatation.

Atropine relieved the attacks primarily through its interference with the vagal reflex and secondarily by its relief of the cardiospasm.

The patient was receiving full therapeutic doses of digitalis on both occasions when spontaneous attacks occurred.

Observations From Study of the Patient While on Full Therapeutic Doses of Digitalis Without X-ray Evidence of Esophageal Dilatation or Clinical Symptoms.—These studies were made with the use of a Miller-Abbott tube inserted in the

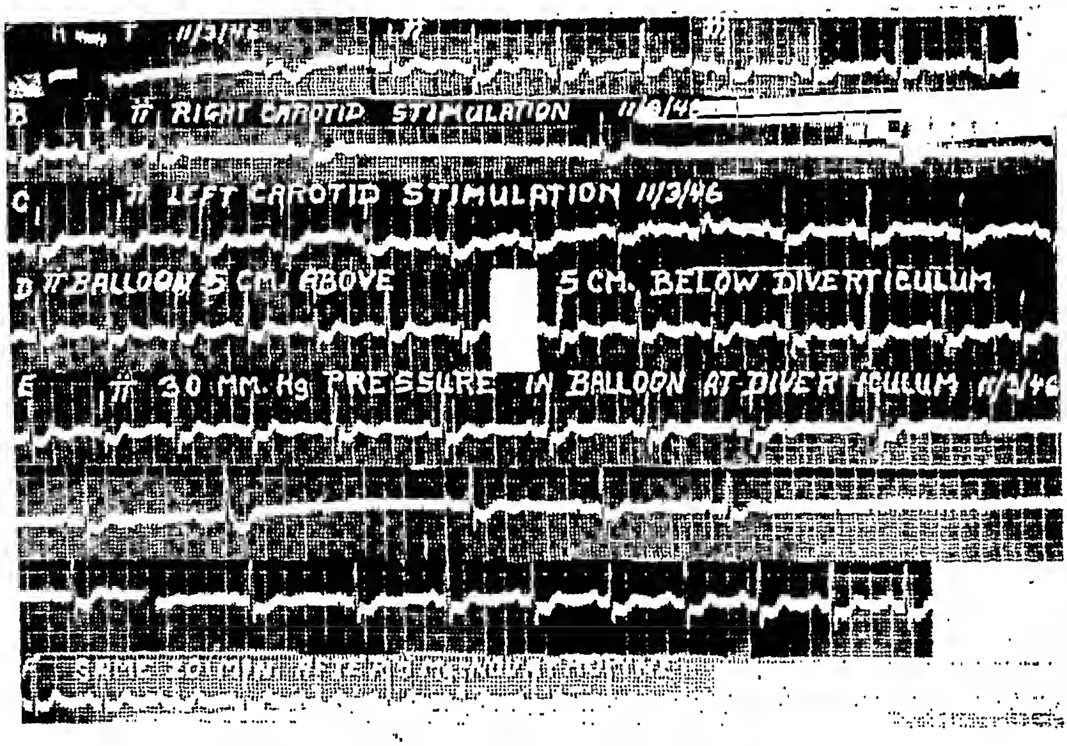

Fig. 2.—Electrocardiogram taken Nov. 3, 1946. Patient on digitalis. No evidence of esophageal dilatation or clinical symptoms. Tracings taken with Miller-Abbott tube in esophagus.

A, Leads I, II, and III after insertion of the tube.

B, Lead II during right carotid sinus stimulation. Sinus arrest with development of slow idioventricular rhythm is present.

C, Lead II during left carotid sinus stimulation. No change in the rate or rhythm is noted.

D, Lead II with the balloon in the esophagus 5.0 cm. above and below the level of the diverticulum and distended with air to a pressure of 80 mm. of mercury. No change in the rate or rhythm is noted in either tracing.

E, Continuous tracing of Lead II with the balloon at the level of the diverticulum distended with air to a pressure of 30 mm. of mercury. There is depression of the sinoauricular node, low-grade atrioventricular block, and occasional cycles of ventricular escape.

F, Lead II twenty minutes after subcutaneous administration of 5.0 mg. of novatropine with the balloon at the level of the diverticulum distended with air to a pressure of 120 millimeters of mercury. The rate and rhythm of the heart are unaltered.

esophagus and inflated by a bulb. The pressure in the balloon was measured by a mercury manometer attached to the Miller-Abbott tube by means of a rubber T tube. Electrocardiograms were routinely recorded, Lead II being used.

Right carotid sinus pressure (Fig. 2,*B*) produced sinus arrest with the development of a slow, irregular idioventricular rhythm. Pressure was released when vertigo became severe.

Left carotid sinus pressure produced no appreciable symptoms or electrocardiographic changes (Fig. 2,*C*).

When the balloon was inserted in the esophagus a distance of 5.0 cm. above or below the diverticulum and inflated with air to a pressure of 80 mm. Hg, there was no appreciable alteration of the heart rate or rhythm (Fig. 2,*D*). The patient's only complaint was uncomfortable substernal fullness or distress.

At the level of the diverticulum, distension of the balloon to a pressure of only 30 mm. Hg produced vertigo, pallor, depression of the sinoauricular node, and low-grade atrioventricular block with occasional cycles of ventricular escape (Fig. 2,*E*).

Atropine sulfate or novatropine, given subcutaneously or orally, effectively prevented the development of bradycardia or arrhythmia on inflation of the

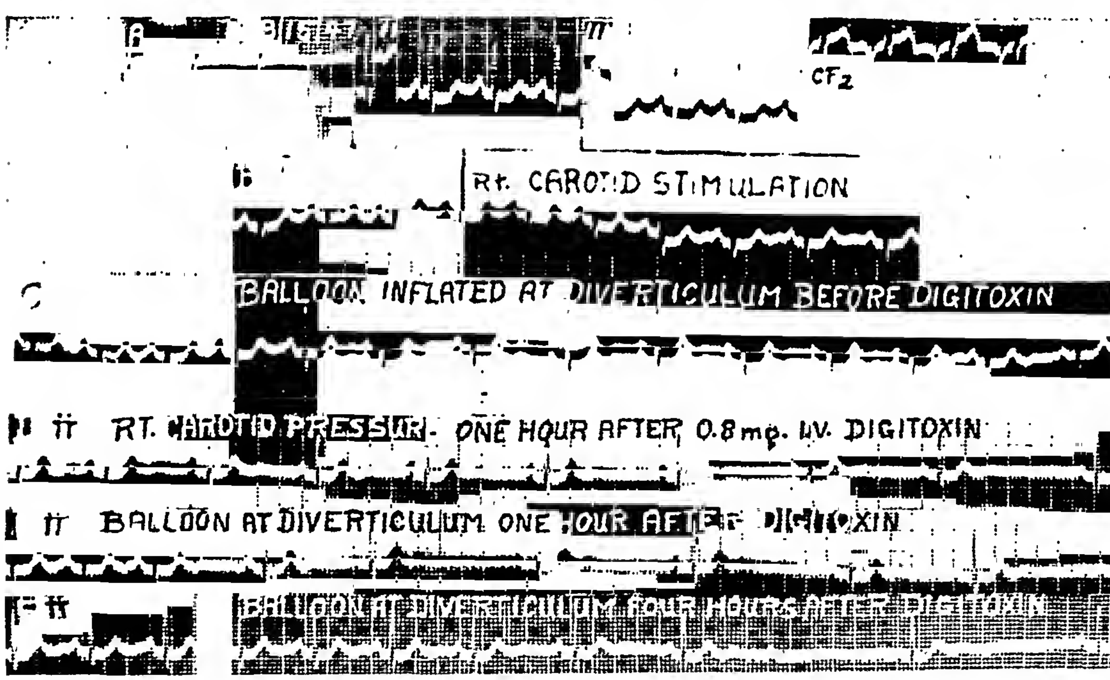

Fig. 3.—Electrocardiograms taken March 15, 1947, three weeks after digitalis was discontinued.

A, Leads I, II, III, and CF_2 with the balloon inserted in the esophagus but not distended with air.

B, Lead II during right carotid sinus stimulation. Stimulation was applied at the time of the broad vertical line on the tracing. No change in rate or rhythm is noted.

C, Lead II with the balloon at the level of the diverticulum and inflated with 100 c.c. of air. There is slowing of the heart rate from 100 to 60 beats per minute and minor alterations of the *P*, probably evidence of downward displacement of the seat of impulse formation in the node.

D, Lead II showing the effect of right carotid sinus stimulation one hour after intravenous administration of 0.8 mg. of digitoxin. Note the increased cardiac slowing.

E, Lead II taken immediately after *D*, with the balloon at the level of the diverticulum and inflated with 80 c.c. of air. Note the marked bradycardia and changes in the form of the *P*.

F, Lead II taken four hours after the digitoxin, with the balloon at the same level but inflated with only 65 c.c. of air. Note the redevelopment of the changes noted in Fig. 2, *E*.

balloon. Fig. 2,*F* is a tracing taken twenty minutes after 5.0 mg. of novatropine had been administered subcutaneously with the balloon at the level of the diverticulum and inflated to a pressure of 120 mm. of mercury.

Swallowing cold water produced changes similar to those induced by right carotid sinus pressure or inflation of the balloon at the level of the diverticulum (Fig. 4,*D*).

Observations Made Three Weeks After Digitalis Was Discontinued.—In these later observations, measured amounts of air injected into the bag of the Miller-Abbott tube by syringe were used because of its greater simplicity.

Repeated stimulation of the right carotid sinus produced no symptoms. The cardiac rate slowed from 100 to 75 beats per minute (Fig. 3,*B*).

The balloon, inserted to the level of the diverticulum and distended with 100 c.c. of air, produced no symptoms. There was slowing of the heart rate from 100 to 60 beats per minute (Fig. 3,*C*). The change in the P wave may be considered evidence of downward displacement of the seat of impulse formation from its usual site in the sinus node.

Observations Following the Intravenous Administration of 0.8 Mg. of Digitoxin.—Right carotid sinus pressure, one hour after administration of the digitoxin, produced mild vertigo and reduction in the heart rate from 90 to 37 beats per minute. The electrocardiogram showed downward displacement of the site of impulse formation (Fig. 3,*D*).

The balloon inserted to the level of the diverticulum and distended with 80 c.c. of air one hour after administration of the digitoxin produced mild vertigo. The heart rate was reduced from 90 to 37 beats per minute. The electrocardiogram again showed downward displacement of the site of impulse formation but no atrioventricular dissociation (Fig. 3,*E*).

Inflation of the balloon with 65 c.c. of air at the level of the diverticulum four hours after administration of the digitoxin produced marked vertigo, pallor, and a slow, irregular heart rate. The electrocardiogram revealed sinus depression, downward displacement of the site of impulse formation, and atrioventricular block.

Observations Following the Subcutaneous Administration of 1.0 c.c. of Adrenalin (1:1,000 Solution) Four Hours After the Digitoxin.—Stimulation of the right carotid sinus fifteen minutes after administration of adrenalin was associated with an increase in the heart rate from 100 to 150 beats per minute with a normal sinus mechanism (Fig. 4,*A* and *B*). Left carotid sinus stimulation immediately thereafter produced no significant change in the heart rate (Fig. 4,*C*). This is a single observation and is included because it is so unusual and because the patient displayed no noticeable increase in apprehension at the time of the test. The observations were not repeated with adrenalin because of substernal distress caused by the dosage employed.

Inflation of the balloon with 100 c.c. of air at the level of the diverticulum approximately twenty-five minutes after 1.0 c.c. of 1:1,000 solution of adrenalin

had been administered subcutaneously caused no appreciable slowing of the heart rate. There were a few multifocal premature beats of supraventricular and ventricular origin.

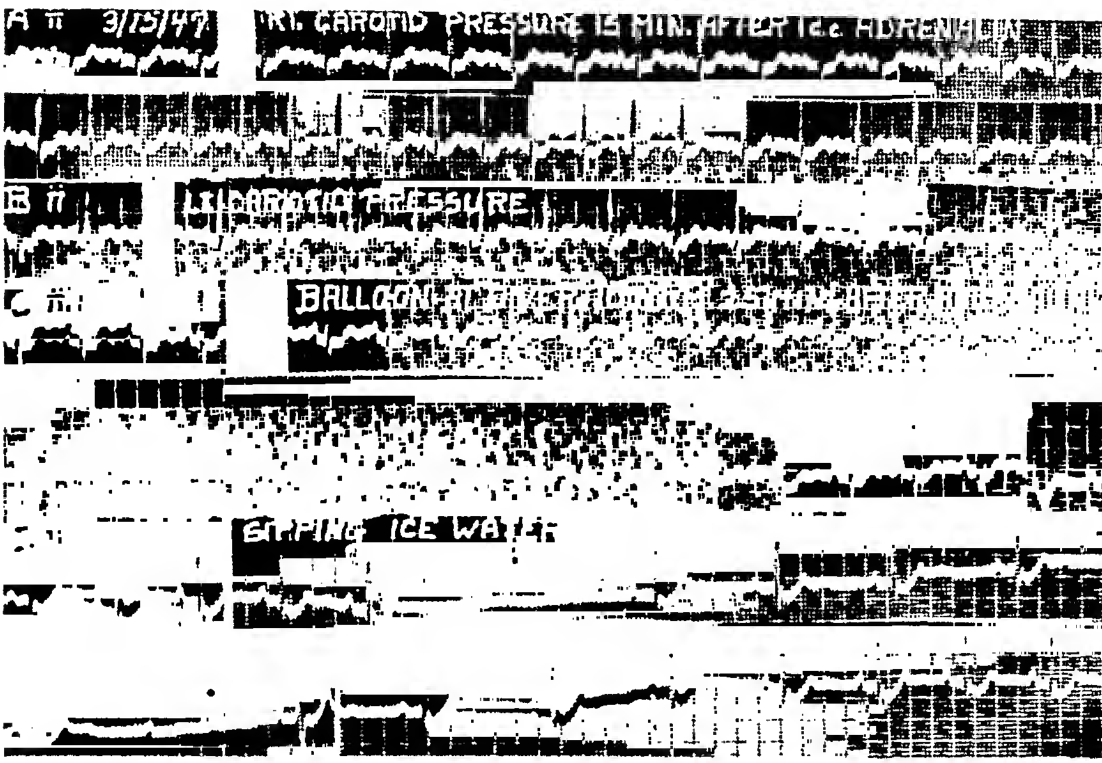

Fig. 4.—Electrocardiograms taken March 15, 1947, after completion of the observations in Fig. 3 and following the administration of 1 c.c. of 1:1,000 solution of adrenalin hydrochloride subcutaneously. The broad vertical lines indicate the point of stimulation or balloon distention.

A, Lead II showing the effect of right carotid sinus stimulation fifteen minutes after adrenalin. The two strips are continuous and show an increase in the sinus rate from 100 to 150 beats per minute.

B, Lead II taken immediately after *A*. Left carotid sinus stimulation had no effect upon the rate.

C, Lead II twenty-five minutes after adrenalin, with the balloon at the level of the diverticulum and inflated with 100 c.c. of air. There is no appreciable effect on the heart rate. A few supraventricular and ventricular premature beats may be noted.

D, Lead II taken March 20, 1947, while the patient was on a maintenance dose of digitalis. This shows the effect of sipping ice water. The two strips are continuous. Periods of sinus arrest, sinus slowing, and atrioventricular block are seen.

DISCUSSION

An extensive literature attests the interest shown in the various mechanisms responsible for the cardiac slowing or arrest producing the Adams-Stokes syndrome.

These conduction defects have been produced experimentally in animals or demonstrated in man in association with interruption of the anatomic integrity of the conduction system by congenital defect, trauma, gummata, various granulomata or other focal infectious lesions, tumors, necrosis, or fibrosis following myocardial infarction. At times the defect is physiological and reversible, the interruption being due to inflammatory lesions which resolve without tissue

destruction; rheumatic fever, diphtheria, and, less commonly, other infections have been implicated. Transient changes in the irritability of the conducting tissue have been demonstrated in asphyxia, after poisoning by various agents such as digitalis, quinidine, and strophanthus, in ischemia secondary to coronary insufficiency from any cause, and after cooling of the esophagus locally in the region of the auricles and junctional tissue. In a large group, reflex vagal stimulation is the important factor, the afferent portion of the reflex arc being by way of the cerebral, sympathetic, glossopharyngeal, or vagus nerves.

It appears likely that in many instances several of these factors operate concomitantly and frequently a summation of two or more is responsible for the development of conduction defects of sufficient degree to produce attacks. Such a summation effect was necessary to produce attacks in the patient described in this report. Digitalis in therapeutic or toxic doses did not produce spontaneous attacks but did sensitize the patient so that cardiospasm with resultant esophageal dilatation and distension of the esophageal diverticulum would produce spontaneous attacks. Artificial esophageal distention, the sipping of cold water, and right carotid sinus stimulation then produced minor clinical attacks with characteristic electrocardiographic conduction disturbances. It is possible that concomitant arteriosclerotic heart disease was an additional factor and by virtue of coronary insufficiency produced ischemia of the junctional tissue. The possible ischemic effect of coronary insufficiency, induced or aggravated by the coronary constrictor effect of vagal stimulation and digitalis, must also be considered.

Critical evaluation of the presence and relative importance of the many possible mechanisms is so difficult that one must be extremely cautious in ascribing the cause of the Adams-Stokes syndrome to any single factor. The possibility of multiple factors and their possible summation effect must always be considered. The disclosure of a surgically correctable source of a hypersensitive reflex in a patient with Adams-Stokes attacks may be a concomitant finding unrelated to the factor or factors producing the spontaneous attacks. This has accounted for some of the poor results from surgical treatment which we have seen. Before any surgical intervention is considered it must be shown that the reflex in question is responsible for initiating the spontaneous attacks, or is a summating factor associated with others which are incorrectable by such simple procedures as omission of a drug or resolution of an inflammatory lesion.

There are many unanswered questions in the problem of hyperirritable vagal reflexes which are raised again in these studies. The variation in tonus of the different autonomic reflexes in the same person in health or disease is poorly understood. The point of increased sensitivity of the reflex, whether sensory, central, or motor, is unsettled. The point or points of action of drugs such as digitalis in effecting the sensitivity of the reflex is not clear. The relation of carotid sinus hypersensitivity to arteriosclerosis is well recognized, but the reasons for this association are not clear. The effects of drugs or of the ischemia of arteriosclerosis may be central, on the motor endings, or on the conducting system itself. The hypersensitive reflex is then more apparent than real, a previously subeffective reflex becoming effective because of increased irritability

of the central nuclei or conducting system. Finally, the single observations on the effect of adrenalin are presented as a matter of interest with no attempt at explanation and no knowledge of whether repetition of the experiment would produce similar results.

CONCLUSIONS

1. A case of Adams-Stokes syndrome due to a vagovagal reflex induced by stimulation of an esophageal diverticulum is reported.
2. The summation effect of digitalis upon the vagovagal reflex and carotid sinus-vagal reflex necessary to produce the Adams-Stokes syndrome is described.
3. The probable frequency of multiple precipitating factors and their possible summation as the essential mechanism in the production of attacks is discussed.
4. Radical treatment should not be contemplated until easily corrected toxic or infectious causes have been eliminated. The reflex to be attacked radically must have been proved to be the sole precipitating factor, or the sole correctable summation factor, and not a concomitant reflex contributing no part to the spontaneous attacks.
5. Consideration of these possibilities will prevent certain of the surgical procedures which prove to be therapeutic failures.

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Abstracts and Reviews

Selected Abstracts

Gilliatt, R. W.: Vaso-constriction in the Finger After Deep Inspiration. J. Physiol. 107:76 (Jan.), 1948.

Reflex vasoconstriction after a deep thoracic inspiration has been reported by various investigators. It was the author's purpose to determine whether this response was initiated by a transient fall in blood pressure during the breath holding and mediated by the carotid sinus or some other pressoreceptor area. The work was carried out with a finger plethysmograph and a method of recording blood pressures continuously.

During a deep inspiration systolic pressure fell in all subjects, and then during the subsequent expiration a rise occurred which lasted for three or four heart beats. Following this there was a return to the control level. A diminution of finger volume invariably took place approximately three seconds after a deep inspiration.

The author concluded that inspiratory vasoconstriction was not a pressor reflex initiated by the fall in blood pressure which accompanied inspiration. However, he was unable to cast any light on the actual mechanism responsible for the reflex.

ABRAMSON.

Philipsborn, H. F., Jr., and Gibson, S.: Paroxysmal Tachycardia; Report of Two Cases Treated With Acetylcholine Bromide. Pediatrics 1:205 (Feb.), 1948.

Two cases of supraventricular paroxysmal tachycardia in infants are presented. The authors obtained successful therapeutic results with digitalis in their previous ten cases with this type of arrhythmia. However, in Case 1, a 1-month-old infant, to a total dosage of 0.375 Gm. of Digifolin, given intramuscularly and intravenously, failed to stop the supraventricular paroxysmal tachycardia. When this patient was admitted to the hospital cyanosis, tachycardia, and enlargement of the liver to the iliac crest were striking. During digitalis therapy edema of the lower extremities appeared; the baby became comatose, and convulsions occurred. The intravenous injection of 1.0 mg. of acetylcholine bromide restored sinus rhythm a few seconds after the injection, and normal rhythm persisted until death occurred fourteen hours later as a result of extensive cerebral hemorrhage. The heart was normal.

An infant 3 weeks of age (Case 2) was well until three days before hospital admission when she cried out suddenly and became pale and cyanotic. When examined, she had a supraventricular paroxysmal tachycardia with a rate of 360 per minute and was thought to be moribund. Acetylcholine bromide was given intravenously in increasing quantities of 1.0 mg., 2.0 mg., and 4.0 milligrams. With the latter injection, sinus bradycardia followed by sinus tachycardia occurred and rapid improvement in the child's condition resulted.

Acetylcholine bromide is a powerful "parasympathomimetic" agent and must be used cautiously, with atropine sulfate ready for intravenous injection. It is not advocated in lieu of digitalis but only if digitalis fails to convert the arrhythmia to normal rhythm, or in urgent cases where immediate relief is indicated. The authors believe that this is the first report of the intravenous use of acetylcholine bromide in infants for the treatment of paroxysmal tachycardia.

JOHNSON.

Hanlon, C. R., and Blalock, A.: Complete Transposition of the Aorta and the Pulmonary Artery; Experimental Observation on Various Shunts After Corrective Procedures. Ann. Surg. **127**:385 (March), 1948.

The complete transposition of the aorta and the pulmonary artery is a relatively infrequent congenital anomaly. The condition in its pure form is described as the aorta arising from the right ventricle and the pulmonary artery from the left ventricle so that the systemic circulation and the pulmonary circulation are completely independent of one another. When no other abnormality is associated with this lesion, life is impossible. However, a number of anomalies, such as a patent interauricular septal defect, patent interventricular septal defect, and patent ductus arteriosus have been found in this condition in 123 cases. In this group, the average duration of life was nineteen months. These other defects make possible a mixture of blood between the right and left ventricles so that there is some oxygenation.

The authors considered various means by which this condition might be helped and carried out experiments in the dog in which the superior pulmonary veins are joined to the right auricle by suture in one group of animals and to the superior vena cava in another group. A special clamp which does not interrupt the main flow of blood through the auricle and superior vena cava is employed during the construction of the anastomosis. They found that the technical aspect of both procedures is not particularly difficult. However, in a group of ten dogs having anastomoses between the pulmonary veins and the right auricle, only four of the anastomoses were entirely satisfactory. In the other six, either marked constriction or complete occlusion occurred. On the other hand, when the pulmonary veins were anastomosed to the superior vena cava at the opening of the azygos vein in fifteen animals, thirteen survived for a sufficient length of time to make evaluation worth-while, and ten of these showed excellent results. Of the three failures, technical difficulties were experienced at the time of operation.

The authors conclude that "anastomosis of the pulmonary veins to the superior vena cava appears feasible in man and offers one possible approach to the surgical treatment of complete transposition of the great cardiac arteries."

LORD.

Arnott, W. M., and Macfie, J. M.: Effect of Ulnar Nerve Block on Blood Flow in the Reflexly Vasodilated Digit. J. Physiol. **107**:233 (March), 1948.

Although it has been settled that vasoconstrictor fibers leading to the skin are present in mixed peripheral nerves, the existence of comparable vasodilator fibers is still in doubt. In an attempt to elucidate this problem, the authors studied the reactions of the ulnar nerve in man. First they determined heat elimination from the distal phalanges of the fifth digits following abolition of vasoconstrictor tone by means of body heating; then they compared these results with those observed after both removal of vasoconstrictor tone and blocking of the ulnar fibers to the fifth digits with procaine. Ulnar block did not alter the heat elimination. Furthermore, the reduction in heat elimination produced by exposure of a reflexly vasodilated subject to a low environmental temperature was also not materially affected by ulnar blocking. From such evidence, the authors concluded that no specific nervous vasodilator activity is present in the ulnar nerve in man.

ABRAMSON.

Taussig, H. B.: Tetralogy of Fallot: Especially the Care of the Cyanotic Infant and Child. Pediatrics **32**:307 (March), 1948.

The purpose of this paper is to discuss the medical care of the cyanotic infant and the means of aiding an infant to survive until he is old enough to withstand operation. The ideal age for operation in patients with the tetralogy of Fallot is 5 to 9 years, when there is a 90 per cent chance of improvement as a result of surgical therapy. In infants the operative mortality is greatly increased and approaches 30 per cent. This operation should be postponed, if at all possible, until childhood.

Cyanosis may not be apparent for six months or longer if the ductus arteriosus remains patent. The initial complaint may be failure to gain weight, and these infants often present

difficult feeding problems. Small, frequent feedings may be helpful and cereals and vegetables in small amounts may be tolerated better than a large amount of milk. Episodes of severe paroxysmal dyspnea are common and are best treated by placing of the infant in the knee-chest position. If relief is not obtained immediately, morphine in dosage of 1.0 mg. per 5 kilograms of body weight should be given. This is almost specific for the relief of paroxysmal dyspnea due to inadequate blood flow.

It is important to remember that anemia may be present in these infants. With anemia the infant's color is less cyanotic but there is less available oxygenated hemoglobin and the oxygen carriage in the blood is greatly lessened. Infants with persistent cyanosis and moderately low red cell count may be helped with repeated small transfusions.

Adequate fluid intake is important in the presence of polycythemia because it lessens the danger of cerebral thrombosis. Infants should receive 800 to 1,000 c.c., children, 1,500 to 2,000 c.c., and adults, 2,500 to 4,000 c.c. of fluid daily. Since convulsions or severe headache may be a precursor of impending cerebral thrombosis, fluids should be forced in patients presenting such manifestations. If paresis or hemiplegia occurs, venesection and replacement by saline or glucose solution, oxygen therapy, and heparin therapy are indicated. With prompt therapy residual hemiplegia can be prevented in most instances.

If the number of episodes of paroxysmal dyspnea is lessening or if attacks can be relieved by the knee-chest position, there is less risk in the postponement of operation than in early operation.

JOHNSON.

Nichamin, S. J.: Stokes-Adams Syndrome Associated With Complete Congenital Heart Block in Infancy and Childhood. Pediatrics 32:327 (March), 1948.

Stokes-Adams snydrome is an uncommon clinical condition in infancy and childhood. Syncopal attacks associated with bradycardia early in life should suggest congenital heart block. It is stated that a slow ventricular beat is essential for the Stokes-Adams attack, for as the diastolic pressure falls during the long interval between beats, there is a diminution in cerebral blood supply. The anoxia may be a factor in producing the convulsive disorder. The primary differential diagnosis is from idiopathic epilepsy. There is always the possibility of sudden death during the attack. Because of the anatomic anomalies of the conduction system in congenital complete heart block, drugs are probably of no value.

A case is reported of a child, first seen at 19 months of age, with a convulsion and a pulse rate of 40 beats per minute, who showed complete A-V heart block. The heart was enlarged and the hilar markings were prominent. The electroencephalogram was considered to be an unstable normal.

JOHNSON.

Lord, J. W.: Arterial and Venous Hypertensive States Benefitted by Surgical Intervention. Surgery 23:550 (March), 1948.

The author points out that there are three hypertensive states which can be aided to a greater or lesser degree by surgical intervention. The first one, coarctation of the aorta, in favorable cases, can be returned to normal by removal of the stenotic segment and end-to-end anastomosis. The operation is tolerated well and the elevated blood pressure in the arms returns to normal and the low blood pressures in the legs rise to levels above those in the arms.

The second, essential and malignant arterial hypertension, is benefitted in the majority of cases by thoracolumbar sympathectomy, although only a small percentage of patients have normal blood pressures after operation. A significant reduction occurs in approximately 75 per cent of the patients operated upon. When careful selection of patients is carried out, the mortality as a result of the operation is extremely low.

The third condition which may be significantly aided by a variety of surgical procedures is that of portal hypertension, whether it is due to intrahepatic block of the portal vein (cirrhosis of the liver) or extrahepatic block of the portal vein (Banti's syndrome). Patients with portal hypertension frequently have massive gastrointestinal hemorrhage from esophageal varices.

The operation, when successful, lowers the pressure considerably in the portal system, which in turn improves the prognosis in this group of patients.

LORD.

Thompson, W. P., and Jellen, J.: Heart Size in Four by Five Inch Films. Am. Rev. Tuberc. 57:379 (April), 1948.

One hundred ten individuals who were studied clinically were selected to represent small normal heart size, average normal heart size, and slight, moderate, and marked enlargement of the heart. In each individual, standard and miniature films were made in full inspiration. Miniature films made at a short target-film distance of about 43 inches introduce relative magnification of the heart, as compared with teleroentgenograms made at the usual distance of 72 inches. On the average, the transverse diameter of the heart was 3.701 times greater in the standard than in the miniature films; 3.7 is, therefore the conversion factor when comparison is made between the two techniques. The cases studied show that this method can be used as reliably for cardiac measurement as the standard 14 by 17 inch teleroentgenogram. The conversion factor of 3.7 may be used to multiply the transverse diameter found in 4 by 5 inch films made at a distance of 43 inches and the result then applied to the standard prediction tables in general use. Survey films are made during full inspiration while the tables generally apply to films made at the end of normal quiet inspiration. Thus, a heart which appears enlarged by the table will, in fact, almost certainly be enlarged.

A study was also made of the cardiothoracic ratio. When a cardiothoracic ratio of 50 per cent was accepted as the upper limit of normal, the correlation was not good. In ninety-nine cases in which the cardiothoracic ratio could be compared by the two techniques, both the table method and the cardiothoracic ratio agreed in indicating enlargement or lack of enlargement in seventy-seven cases. In the remaining cases one method indicated enlargement while the other did not. These authors admit that the use of the cardiothoracic ratio will omit a number of patients with cardiac enlargement and will lead to suspicion in a number of patients with normal hearts.

The conclusion is drawn that a diagnosis of heart disease may not be made on the basis of survey films alone, and that suspected cases should be studied clinically and by the use of standard 14 by 17 inch teleroentgenograms.

BELLET.

Hinton, J. W., and Lord, J. W., Jr.: The Selection of Patients for Thoracolumbar Sympathectomy. Ann. Surg. 127:681 (April), 1948.

As a result of their clinical experience with 375 hypertensive patients undergoing thoracolumbar sympathectomies, the authors arrived at a group of principles or rules which enabled them to eliminate the majority of patients who were bad risks. In general, patients who show wide-spread, extensive involvement of the brain, eyes, heart, and kidneys should not be operated upon. Patients with persistent elevation of the blood urea nitrogen and nonprotein nitrogen because of marked impairment of renal function are also bad subjects for operation. A third group of patients manifesting mental confusion which seems to be on an organic basis prove to be poor risks. Finally, patients whose cardiac status is one of unremitting congestive failure should be rejected.

LORD.

Sciarini, L. S., Ackerman, E. M., and Salter, W. T.: The Response of Isolated Hypodynamic Myocardium to Inotropic Drugs. J. Pharmacol. & Exper. Therap. 92:432 (April), 1948.

The authors used the papillary muscle from the right ventricle of a cat which was made to contract until weakened and then was subjected to small doses of ouabain so that the "therapeutic" effect of increasing its strength of contraction could be calibrated. This type of calibration differs from the standard assay methods in that the toxicity of the drug to be assayed does not

enter into the calibration and only positive inotropic effect of the drug is measured. Variable factors such as absorption, distribution, excretion, and destruction play no part in the calibration.

After calibration with a ouabain standard, each individual papillary muscle can be assigned its own muscle constant, a. Then the fractional response, R, to any glycoside, G, may be established by an equation:

$$\log G + \log M + \log a = 0.5 \log [R(1\text{-}R)]$$

where $\log M$ is the negative log potency of the glycoside.

GODFREY.

White, W. F., Belford, J., and Salter, W. T.: Isodynamic Equivalents of Digitoxin Cogenersas Tested on Hypodynamic Myocardium. J. Pharmacol. & Exper. Therap. 92:443 (April), 1948.

Results obtained by the methods described in the preceding abstract (J. Pharmacol & Exper. Therap. 92:432, 1948) were compared with the potency values assigned to various cardiac glycosides by the standard assay method (lethal effect on the intact cat).

The over-all results showed a surprising similarity, indicating that despite the obvious defects in the cat assay methods, the available data on the potency of the various cardiac glycosides are probably very nearly correct.

GODFREY.

Cauldwell, E. W., Siekert, R. G., Lininger, R. E., and Anson, B. J.: The Bronchial Arteries: An Anatomic Study of 150 Human Cadavers. Surg., Gynec. & Obst. 86:395 (April), 1948.

In an extensive study of the bronchial arteries in 150 human cadavers, the authors found that there were essentially nine different types of bronchial arterial supply. In approximately 80 per cent the supply was represented by either one or two pairs of bronchial arteries arising from the descending aorta. In some instances as many as four bronchial arteries were found on the left side, whereas usually only one or two were found on the right. The mid-portion of the esophagus receives the major portion of its blood supply from the adjacent bronchial arteries.

LORD.

Shumacker, H. B., Jr., Speigel, I. J., and Upjohn, R. H.: Causalgia. II. The Signs and Symptoms, With Particular Reference to Vasomotor Disturbances. Surg., Gynec. & Obst. 86:452 (April), 1948.

Causalgia follows partial injury of peripheral nerves and is characterized by a burning type of pain, associated with signs of emotional instability and irritability, nutritional changes, and either vasoconstriction or vasodilatation in the affected limb.

The authors present their findings in a group of ninety male patients suffering from this condition. In every instance one or more of the major nerves to the extremities were injured. In almost all of the cases pain was burning in character, although frequently associated with other types of discomfort. Almost without exception the pain was made more intense by the use of the part or by tapping or touching the affected hand or foot. Placing the limb in dependency aggravated the condition. In all instances the symptoms were localized in the hand or foot, and it was commonly limited to, or was more intense in the distribution of the injured nerve.

Of the number on whom skin temperature studies were done, in about one-third the digits of the affected hand or foot were almost equal in temperature to those of the opposite normal side. In approximately one-fifth of the patients the involved limb was colder than the other. In the remainder the digital skin temperature of the injured extremity was distinctly higher than that of the other. It would seem, then, that the pain was unrelated to the state of vasomotor tonus, since it was experienced in the presence of increased, decreased, or relatively normal vasomotor tonus.

ABRAMSON

Fowler, N. O., Jr., and Failey, R. B., Jr.: Perforation of the Infarcted Interventricular Septum; Report of Two Cases, One Diagnosed Ante-mortem. Am. J. M. Sc. **215**:534 (May), 1948.

Including the authors' two cases, a total of fifty-six cases of infarcted interventricular septum with perforation have been found in the literature; fifteen of these were diagnosed ante mortem. In thirty-eight patients whose survival time was known, thirty-one survived less than one month, thirty-seven less than one year, and one survived four years and ten months. Forty-three patients of forty-five examined showed systolic murmurs, usually maximal to the left of the lower sternum; twenty-two showed systolic thrills; only three showed diastolic murmurs.

The diagnosis should be suspected in any patient known to have a myocardial infarction who suddenly develops a systolic murmur and thrill to the left of the lower sternum. The only condition likely to be confused is rupture of a papillary muscle following cardiac infarction. In this condition the murmurs are louder and nearer the apex, and the ensuing failure is left-sided rather than right-sided.

DURANT.

Baer, S., Heine, W. I., and Gelfond, D. B.: The Use of Vitamin E in Heart Disease. Am. J. M. Sc. **215**:542 (May), 1948.

Early in 1946 attention was called by Vogelsang and Shute to the marked improvement resulting from the administration of vitamin E to patients with various forms of heart disease. Considerable publicity was given to the phenomenal therapeutic results claimed in congestive heart disease and angina pectoris by these authors. Shute was quoted as saying: "We have not learned of a single failure. The percentage of success is remarkable." Patients began to request this treatment from physicians, and less scrupulous drug houses, in their attempts to sell preparations of alpha-tocopherol, quoted entire paragraphs from the articles recommending vitamin E.

The authors began their study of vitamin E in heart disease in August, 1946, and their report includes observations on twenty-two patients. Doses of 300 to 400 mg. daily were given to eleven patients with congestive heart failure, five patients with angina pectoris, and six patients with hypertensive and, or arteriosclerotic heart disease. In no case was there any demonstrable effect on the electrocardiogram, orthodiagram, or blood pressure. None of the twenty-two patients was markedly or moderately improved. Six patients were questionably improved, and the remainder showed no change or became distinctly worse. The results are so at variance with those published that the authors hesitate to recommend the use of vitamin E in heart disease. Certainly much more scientific work must be done in this field before suggestions are made that so appreciably alter our present forms of cardiac therapy.

DURANT.

Hinchley, J. J., Hines, E. A., Jr., and Ghormley, R. K.: Osteoporosis Occurring During Potassium Thiocyanate Therapy for Hypertensive Disease. Am. J. M. Sc. **215**:548 (May), 1948.

Osteoporosis with arthralgia was noted in 2 per cent of patients receiving potassium thiocyanate therapy for hypertension. Of eleven such patients, the age ranged from 46 to 68 years. There were six women and five men. Onset of symptoms associated with the osteoporosis generally occurred within three to six months after administration of the drug was started. They consisted of (1) pain on use of the extremity which began insidiously and gradually increased in severity, and (2) subsequent mild swelling of the joint or joints involved, but with no acute inflammatory reaction. The severe cases simulated those of extensive post-traumatic osteoporosis. Roentgenograms, which were limited to the involved regions, revealed mild to marked diffuse osteoporosis. No similar syndrome was found in more than 5,000 consecutive cases of hypertension in which this drug was not used.

Evidence at hand seems to suggest slight and prolonged interference with calcium metabolism as a possible mechanism for production of the syndrome. It appears that adequate calcium intake should be assured for persons who are taking potassium thiocyanate. Use of this drug may be contraindicated in the presence of bone malacia, such as senile osteoporosis or osteitis deformans;

likewise its use may be inadvisable in the presence of fracture, not with regard to union of the fracture, but because any interference with calcium metabolism in the presence of increased calcium requirement might precipitate osteoporosis.

DURANT.

Harman, J. W.: The Significance of Local Vascular Phenomena in the Production of Ischaemic Necrosis in Skeletal Muscle. Am. J. Path. 24:625 (May), 1948.

As a sequence to his previous work on the nature of the ischemic degeneration of skeletal muscle, Harman studied the vascular phenomena associated with both acute and necrotic ischemic necrosis of skeletal muscle. In discussing the classical clinical studies on this problem by Volkman down to Leriche, the author notes that arterial and venous lesions and vascular spasm have been considered the major factors without any consideration of capillary function which is so important in skeletal muscle. It is particularly important because of the unique gradient of permeability in muscle capillaries.

Harman produced complete ischemia in the right hind legs of rabbits by use of tourniquets. This was proved by the failure of Fluoresite injected intravenously to pass distal to the tourniquet. Angiography was employed on animals thus made locally ischemic for four to four and one-half hours· also after release of the obstruction at periods varying from three to forty-eight hours. Thorotrast and India ink were used, the animals being sacrificed within a few minutes and their extensor and flexor muscles excised from both the normal and ischemic legs. Tissue from both groups was fixed in formalin, then cleared by the Spalteholz method for direct visualization of injected vessels. Angiography consisted of two successive injections, 5 c.c. each of Thorotrast, quickly followed by x-ray exposure, a third exposure being made one minute after completion of the last injection.

Regardless of the duration of the ischemia, the pulse in the great saphenous artery was always palpable on release of the tourniquet. It became less palpable with the accumulation of edema fluid, but it was never obliterated. Angiography verified this continuous postobstruction arterial patency. In ten animals it also showed a definite sequence of visualization. The veins of the ischemic leg would fill but this always was delayed, showing that the retardation was between the arteries and the veins, namely, in the capillary and fine venule sector. India ink injections used as a control showed penetration as far as the small intramuscular arterial branches.

Harman then injected bromphenol blue into one group of rabbits with ischemic right hind legs five minutes after release of the tourniquet. The rabbits of this group were studied one-half hour, three hours, and twenty hours after dye injection, with the muscles of both the ischemic and the normal hind legs exposed for direct visualization. When ischemia had lasted for four hours or longer, passage of dye through the damaged muscles was delayed in both its inception and completion. In the same study applied to a second group of rabbits, in which the dye was injected twenty hours after the release of the tourniquet, the results were strikingly emphasized, all being indicative of a functioning but sluggish intramuscular circulation.

The histologic picture of muscle several hours after the release of vascular obstruction showed profuse infiltration of monocytes and neutrophiles, edema, and various types of extensive degeneration of the muscle. The capillaries were dilated and nonthrombosed, but tightly packed with erythrocytes. The larger arterial and venous channels remained unaltered.

By determination of the weight of the excised muscles from both the ischemic and normal limbs, Harman demonstrated a significant increase in weight, due to edema, most marked in flexor muscles as contrasted with the extensors.

This experimental work was extended to permit observation on the muscle changes as late as fifteen to twenty days following release from ischemia. At this time injection of bromphenol blue revealed late sequelae which were the intense dye staining in shrunken but firm elastic and contractile muscles, weighing less than normal, but free of infarction, all of this in muscles subjected to ischemia for three hours or less. Muscles rendered ischemic for four hours or longer weighed more, contained yellow areas of infarction of variable size, and were electrically nonirritable.

The author points out that these changes differ greatly from those produced by venous occlusion and are similar to those produced by arterial occlusion, yet they occur in the presence of functionally preserved large arteries. He concludes that capillary damage is the basis for the ischemic necrosis of skeletal muscle, especially of the type leading to Volkmann's contracture, and draws an analogy between this and the experimental work of Meneely which showed that abnormal capillary permeability permits progressive myocardial destruction after release of temporary coronary artery occlusion.

This extensive experimental work conclusively removes venous obstruction as a factor in the pathogenesis of ischemic muscle necrosis, yet does not decisively differentiate between arteriolar and capillary damage, a fine point of distinction which may have pharmacologic and therapeutic implication in future studies on this subject.

GOULEY.

Ganem, E. J., and Cahill, G. F.: Pheochromocytomas Coexisting in Adrenal Gland and Retroperitoneal Space, With Sustained Hypertension. New England J. Med. 238:692 (May 13), 1948.

A case of coexisting intra- and extra-adrenal pheochromocytomas in a 12-year-old girl is reported. Profuse sweating, heat intolerance, excessive appetite without weight gain, excessive thirst, fatigue, palpitation, and paresthesias of the hands had been noted for about two years. On examination, undernutrition, emotional instability, warm and moist skin, and tachycardia were found. The blood pressure averaged 180/120 and the pulse, 120 per minute. In the laboratory studies, the basal metabolism ranged from +51 to +67 per cent. The blood iodine was normal. During a nine months' period of observation, the blood pressure rose to 200/150 and papilledema appeared. Lugol's solution was not helpful.

Left adrenal enlargement was then demonstrated by bilateral perirenal air insufflation after urography had shown no abnormality. Improvement followed removal of an intra-adrenal pheochromocytoma. A second tumor mass was suspected at operation, but was not removed. The blood pressure remained pathologically elevated.

It was considered probable that pathologic tissue was still present. This impression was supported by the prompt reduction in blood pressure which followed the intravenous administration of a benzodioxane (1164F). At a second operation, a second tumor was removed from the left retroperitoneal space. Complete recovery followed convalescence. The blood pressure fell to normal and was thereafter not influenced by the injection of 1164F.

Variations in the clinical manifestations of pheochromocytoma are discussed. Importance is placed on perirenal insufflation of air as an aid in the localization of early enlargements of the adrenal gland. The value of nontraumatic surgical technique and of careful administration of adrenalin and adrenal cortical extracts during and after operation is stressed.

KAY.

Hodge, G. B., and Messer, A. L.: The Electrocardiogram in Biliary Tract Disease and During Experimental Biliary Distention: Clinical Observations in 26 Patients. Surg., Gynec. & Obst. 86:617 (May), 1948.

The authors studied the effect on the electrocardiogram of distention of the gall bladder and common duct in twenty-six patients with biliary tract disease during the procedure of removal of the gall bladder and postoperatively in cases of common duct exploration by means of the T tube. They noted in patients with normal cardiovascular systems that there were changes in the electrocardiogram in some patients during anesthesia; in others, during the operation. None of these changes suggested myocardial insufficiency. Distention of the gall bladder to a pressure of 100 cm. of water caused an increase in the pulse rate and blood pressure of some patients, whereas in others a decrease occurred. Postoperatively, distention of the common duct by injection of a saline solution to a pressure of 100 cm. of water caused pain in the epigastrium and occasionally pain radiating to the back, but never did the pain simulate that of angina.

The authors conclude that there is no definite electrocardiographic pattern in gall bladder disease and that the changes which occur are variable and are probably coincidental.

LORD.

Adams, H. D.: Surgery of the Major Blood Vessels. Texas State J. Med. 44:10 (May), 1948.

A number of vascular disorders affecting the major vessels lend themselves to treatment by surgical methods. The simplest of these is peripheral arterial embolism. Success in the surgical treatment of this condition depends upon early recognition and immediate embolectomy. Generally approximately one-half of the patients will be saved if this procedure is performed within ten hours after occlusion of the vessel has occurred, while after thirty hours none will be saved. Commonly the embolus will lodge at the various bifurcations of the main vessels. It is necessary not only to remove the embolus, but an attempt must be made to suck out the distal thrombus and establish free back flow of blood and a return of normal arterial pulsations in the peripheral vessels.

Arteriovenous aneurysms of the peripheral arteries are most readily treated by quadruple ligations and excision of the involved segments. This procedure can be carried out in almost any major artery of the body except possibly the carotid and the popliteal arteries. The objection to performing the operation on the carotid artery is the high incidence of cerebral damage which follows, while in the case of the popliteal, generally gangrene of the foot will occur because of the poor collateral circulation around the knee.

In the case of arterial aneurysm, the artery and also the accompanying vein are ligated and the false sac is removed. This method appears to have certain advantages over any type of plastic procedure.

Aside from surgery of the major vessels of the extremities, recently great strides have been made in applying similar principles to the large vessels in the chest. Since a patent ductus arteriosus usually causes death at an early age from congestive heart failure or subacute bacterial endocarditis, attempts have been made to treat the condition surgically by active division of the connecting vessel between aorta and pulmonary artery. Similarly, coarctation of the aorta has been cured either by means of an anastomosis between the proximal divided end of the left subclavian artery and the site of the aorta distal to the coarctation or by end-to-end anastomosis of the aorta after the stenosed portion has been removed. In the case of pulmonary stenosis, the formation of an aortopulmonary fistula or the production of an anastomosis between the right or left subclavian artery with the corresponding pulmonary artery has led to considerable change in the clinical appearance of the patient.

For the relief of symptoms of portal hypertension, it is necessary first to determine whether hepatic or extrahepatic portal obstruction exists. In the intrahepatic type, impaired hepatic function can be demonstrated by the various clinical tests. Gastrointestinal hemorrhage, ascites, or both, or the classical clinical syndrome of Banti's disease are the primary indications for surgical intervention. If there is hypertension in the splenic vein and not in the inferior vena cava, splenectomy and splenorenal anastomosis are effective in stopping the gastrointestinal hemorrhages. If intrahepatic block or extrahepatic portal block high in the liver is present, a portocaval anastomosis or Eck fistula can be carried out.

ABRAMSON.

Nygaard, K. K.: Intermittent Raynaud's Phenomenon Resulting From Nonunited Fracture of the Navicular Bone. Am. J. Surg. 75:834 (June), 1948.

The author reports a case of Raynaud's phenomenon in a patient with a nonunited fracture of the navicular bone. Initially the lesion had been treated with a plaster cast which had been worn for three weeks. For several years after the accident, the patient complained of moderate pain in his hand. Subsequently this increased in severity. At the same time the patient noted that when he performed certain functions involving the affected hand, he would develop a tingling sensation and weakness of the muscles of the hand. Generally associated with these symptoms were episodes of Raynaud's phenomenon involving the fingers. The attacks were not related to a cold environment nor were they precipitated by worry or anxiety. Examination revealed a bony, hard, irregular prominence over the navicular bone which by x-ray was shown to be related to a transverse nonunited fracture of this bone. Following operative interference, the local tender-

ness disappeared and the procedures previously producing the episodes of Raynaud's phenomenon were now no longer effective in this regard.

It is the author's opinion that during weight carrying the pain associated with the impingement of the loose fragments of the navicular bone against the nerve endings in the adventitia of the radial artery was in some way related to the initiation of the Raynaud's phenomenon.

ABRAMSON.

Levy, H., and Boas, E. P.: Vitamin E in Heart Disease. Ann. Int. Med. **28**:1117 (June), 1948.

Thirteen patients were treated with alpha-tocopherol, the daily dosage varying from 200 to 800 milligrams. In most of the patients, plasma levels of alpha-tocopherol were determined while the vitamin was being taken; in some, control levels were also taken before the vitamin was administered. Four of the patients with chronic heart failure responded dramatically to a low-salt diet after large doses of vitamin E had caused no diuresis or improvement in the state of heart failure. There was no evidence whatsoever that this drug affected the pattern, the frequency, the intensity, or the precipitation of anginal pain in five patients with chronic anginal pain with a stable pattern of chest pain related to effort. Likewise, in three cases of angina pectoris, in states of coronary insufficiency characterized by a new pattern of increased frequency and intensity of attacks, often occurring at complete rest, there was no change to be attributed to the use of this vitamin.

WENDKOS.

Caldwell, H. W., and Hadden, F. C.: Carotid Artery Thrombosis: Report of Eight Cases Due to Trauma. Ann. Int. Med. **28**:*1132* (June), *1948*.

During World War II, the ante-mortem diagnosis of post-traumatic thrombosis of a carotid artery was substantiated in six soldiers either at necropsy or at the time of operation. The condition was suspected during life because of the occurrence of various types of paralysis following penetrating or nonpenetrating injuries to the neck. The diagnosis in two other patients who presented similar features during life was established only at necropsy. Recovery in one case was apparently due to the early institution of heparin therapy after the clinical diagnosis was made. The neurological findings are explained by cephalad propagation of the thrombus with resultant occlusion of the external carotid and the branches of the internal carotid including one-half of the circle of Willis, or else by embolism by fragments of the thrombus to the smaller cerebral vessels.

Surgical occlusion of the vessel and possible resection above and below the thrombus is possible if carried out early. The absence of the temporal pulse on the involved side is good confirmatory evidence that the common carotid and possibly the external carotid is occluded. This sign is of value also in indicating to the surgeon the extent to which the carotid vessel must be dissected if surgery is the elected type of therapy. The absence of the right radial pulse may indicate that the subclavian artery is also occluded by the thrombus propagating toward the heart.

It is suggested that exploration of the carotid vessels at autopsy may demonstrate the true etiology of some obscure cases of "apoplexy."

WENDKOS.

Hollander, G., and Mandelbaum, H.: The Treatment of Angina Pectoris With Propylthiouracil. Ann. Int. Med. **28**:1150 (June), 1948.

Ten hypertensive patients with a definite anginal syndrome varying in duration from five months to seven years were treated with 6-propylthiouracil in doses up to 200 mg. a day. Only one of the ten patients was male. The ages of the patients varied from 45 to 62 years. Symptomatic improvement occurred in four cases for a six-month period. The initial basal metabolic rate and the subsequent readings did not determine the final results. Myxedema levels were not necessary for relief of pain since three of the four patients who were relieved of pain had basal metabolic rates within normal limits at the time symptoms were improved. If improvement

did occur, it did so within eight weeks of beginning treatment. The observed, untoward effects of 6-propylthiouracil were a tendency to water retention and intermittent claudication. No toxicity with 6-propylthiouracil, in doses up to 200 mg. a day, was observed.

WENDKOS.

Barden, R. P., and Cooper, D. A.: Peripheral Vascular Disease in the Lungs: Roentgenologic Manifestations. J. A. M. A. 137:584 (June 12), 1948.

The authors review the various disorders which affect the peripheral pulmonary vessels and which may produce roentgenographic changes. The diseases are classified under three categories: (1) Intrinsic disease of the vessel wall (arteriosclerosis and arteriolosclerosis) or obstruction of the vascular lumen (embolism by clot, neoplastic cells, and parasites, and thrombosis, as seen in the leucemias and polycythemia vera). The close association between obliterative vascular changes and pulmonary hypertension, and between obliterative vascular disease and pulmonary emphysema is pointed out. (2) Vascular change secondary to disease of the adjacent parenchyma (acute and chronic pulmonary inflammatory disorders, and neoplasms of the lung). (3) Toxic and hypersensitivity states (sulfonamide poisoning, serum sickness, acute rheumatic fever, lupus erythematosus, periarteritis nodosa, glomerulonephritis, hypoproteinemia, beriberi).

These disorders all bring about increased permeability of the pulmonary capillaries with consequent patchy or massive edema and present the same type of roentgenologic picture.

HANNO.

Peet, M. M., Isberg, E. M., and Bassett, R. C.: Toxemia Superimposed Upon Prepregnant Hypertension Treated by Splanchnicectomy. Surg., Gynec. & Obst. 86:673 (June), 1948.

The authors point out that about 50 per cent of prepregnant hypertensive women can be expected to develop a superimposed toxemia and that one-fourth of these patients are left with higher blood pressure levels and more extensive disease as a result of a toxemic pregnancy. The authors report five patients with hypertension who developed a toxemia during pregnancy. Each of these patients was submitted to bilateral supradiaphragmatic splanchnicectomy with excellent results, including return to normal levels of the blood pressure and relief of the toxemia in two patients. These two patients also continued to do well as long as four years and two years, respectively, after operation. Of the three remaining patients, two were helped moderately and one was a failure. The failure occurred in a patient who exhibited extremely poor renal function and who subsequently died fifteen months after operation.

In the discussion, the authors point out that splanchnicectomy should be performed within the first three weeks of the toxemia in this group of patients. Further, if splanchnicectomy has not relieved the toxemia within three weeks, then the pregnancy should be terminated. The third point made by the authors is that splanchnicectomy should not be employed in patients whose toxemia of pregnancy is associated with marked renal damage.

LORD.

Kiesewetter, W. B., and Schmacker, H. B., Jr.: An Experimental Study of the Comparative Efficacy of Heparin and Dicumarol in the Prevention of Arterial and Venous Thrombosis. Surg., Gynec. & Obst. 86:687 (June), 1948.

In an extensive series of experiments carried out on dogs, the authors developed a technique of effecting thromboses in veins and arteries with great consistency. Approximately 90 per cent of the veins (jugular and femoral), 80 per cent of the small arteries (femoral), and 70 per cent of the large arteries (carotid) were thrombosed by the seventh day following trauma in control animals. In the group treated with heparin a significant reduction in the incidence of thrombosis was noted: 56 per cent of the veins, 6.7 per cent of the small arteries, and 9.5 per cent of the large arteries. In the Dicumarol-treated animals, the incidence of thromboses was 41 per cent of the veins, 50 per cent of the small arteries, and 15.8 per cent of the large arteries.

The authors conclude that anticoagulant therapy is of great value in the prevention of thromboses of veins and arteries subsequent to trauma. However, with the possible exception of the superiority of heparin in the prevention of thrombosis of injured small arteries, the difference between the anticoagulants, heparin and Dicumarol, was not significant.

LORD.

Elkin, D. C., Cooper, F. W., Jr., Rohrer, R. H., Miller, W. B., Jr., Shea, P. C., Jr., and Dennis E. W.: The Study of Peripheral Vascular Disease With Radioactive Isotopes. Part I. Surg., Gynec. & Obst. 87:1 (July), 1948.

The authors utilized radioactive sodium 24 in the investigation of the circulation to the extremities. Two methods were studied. In one, 5 c.c. of the prepared solution was rapidly injected into an antecubital vein and the circulation time to the lower extremity was determined by noting the sudden rapid increase in the rate of count of the Geiger-Mueller detector placed posterior to each gastrocnemius muscle and at the ball of each foot. The figure obtained depended not only upon the flow of blood to the part but also upon the diffusion of sodium chloride from the vessel into the extravascular spaces. The second method consisted of injecting the sodium directly into the gastrocnemius muscle and determining the rate of disappearance of the material as recorded on a detector placed behind the gastrocnemius muscle. The rate of removal depended upon the circulation through the nutrient capillaries.

It is the authors' opinion that with this procedure a means is at hand for determining the relative blood flow to the muscles, since the rapidity of removal of the sodium from this tissue is related to the volume of blood flow locally.

ABRAMSON.

Puddu, V., and Mussafia, A.: Considerations on the Electrocardiogram During Exercise Tests. Acta Cardiol. 2:140, 1947.

Depression of the RS-T segment during exercise in patients with coronary artery disease may be explained by a delay of endocardial repolarization. Occasional elevation of the RS-T segment must be assumed to be the result of a diffusion of the ischemic region toward the epicardial layers. Uprighting of a previously inverted T wave during the test is explained as the result of a balance between two regions, one of which is characterized by delay of repolarization at rest, the other by a normal resting condition which upon exercise becomes equally delayed. A temporary "normalization" of the record must result.

HECHT.

Segers, M.: Interaction Between Auricles and Ventricles. Acta Cardiol. 2:335, 1947.

Three clinical examples are presented in which an interaction between auricles and ventricles could be demonstrated in the presence of complete A-V block. The presence of such interaction in the apparent absence of anatomical pathways may be seen (1) in synchronization of auricular and ventricular beats in instances of complete A-V block; (2) in shortening of P-P intervals in complete A-V block during the ventricular excitation; (3) in alteration of the contour of the P wave in complete block in auricular beats that follow the ventricular complex; (4) in auricular extrasystoles appearing in close relationship to the ventricular beats in A-V block; and (5) in an abnormal duration of the ventricular compensatory pause after ventricular extrasystoles. No physiological explanation has been attempted.

HECHT.

Wallgren, A.: Tuberculous Heart Disease. Acta med. Scandinav. (Suppl.) 196:132, 1947.

Three cases of tuberculous pericarditis are reported. The first, an 8-year-old boy, died of exudative and adhesive pericarditis following fever, erythema nodosum, and a left hilar lesion with enlarged retrocardiac nodes. A left upper lobe caseous pneumonia was found adherent to the pericardial surface. In contrast to this, two boys, 9 and 6 years of age, respectively, developed friction rubs, enlarged cardiac shadows, and altered T waves one month after the onset of febrile

primary tuberculosis of the lung. The cardiac signs persisted about three weeks and were accompanied by increased fever and further elevation of the sedimentation rate. There were no demonstrable cardiac sequellae except a change in the contour of the right auricular border in one boy. This was attributed to a pericardial adhesion. No rheumatic manifestations were recorded in the past histories, nor did any appear for the duration of a three-year follow-up period after the pericarditis. The author compares the situation in his latter two patients with acute "tuberculous-allergic" serofibrinous pleurisy on the basis of the brief course and good prognosis.

SAŸEN.

Graf, W., Moller, T., and Mannheimer, E.: The Continuous Murmur. Acta med. Scandinav. (Suppl.) 196:167, 1947.

Phonocardiographic records in five frequency ranges were recorded simultaneously with Lead II of the electrocardiograph to demonstrate the characteristics and points of maximal intensity of the main types of continuous murmurs: in patent ductus arteriosus, the thyroid murmur of Graves' disease, arteriovenous aneurysm, the fontanel murmur of infants, and the venous hum of children.

The murmur of patent ductus arteriosus began about 0.04 seconds after the first heart sound. The regularity with which it was loudest in the second left intercostal space is stressed, the authors believing that continuous murmurs with their greatest intensities in the third and fourth intercostal spaces or the aortic area indicate other types of anomaly. Three pre- and postoperative phonocardiograms of patients with patency of the ductus arteriosus are reproduced, as well as tracings of a patient thought at operation to have a persistent truncus communis. The continuous murmur in this latter instance was loudest in the third left intercostal space.

The thyroid murmur was studied in thirteen women with Graves' disease and found to have a frequency extending up to 400 to 500 cycles per second. There was frequently a difference in intensity between the two lobes.

Three cases of arteriovenous aneurysm were studied, two intracranial and one at the ankle. The frequencies ranged between 500 and 1000 cycles per second.

One tracing of a fontanel murmur was reproduced. It was recorded both at the anterior fontanel and the external auditory meatus, and was of moderate amplitude in all frequencies between 50 and 500 cycles per second. It was believed to have been produced in the intracranial veins.

The venous hum in the neck was studied in forty children selected from 250 children examined. The incidence of the hum was 42.8 per cent from birth to 3 years, 65.5 per cent between 3 and 6 years, 52.9 per cent between 6 and 9 years, 47.8 per cent between 9 and 12 years, and 30.8 per cent between 12 and 15 years. The intensity was equal on both sides in one-half the cases studied, the remaining half being divided about equally between right and left sides as to maximal intensity. Turning the head to the opposite side increased the intensity of the murmur, as did deep inspiration, while digital compression of the jugular vein made it disappear. These characteristics were illustrated by tracings. The frequency range was 50 to 500 cycles per second but usually was not greater than 400 cycles per second.

SAŸEN.

Akesson, S.: Arterial Orthostatic Anemia With Cardiac Pains. Acta med. Scandinav. (Suppl.) 196:192, 1947.

The author reports a 21-year-old man who developed vague and variable precordial pain and palpitation which became gradually worse for eighteen months and were related to exertion, anxiety, and eating. The blood pressure in recumbency was found to be 135/90 and the pulse, 80 per minute. After the patient had stood for eight minutes, these figures were, respectively, 115/85 and 104 per minute. The heart was normal by fluoroscopy. The electrocardiogram when the patient was recumbent showed slightly low T waves in the limb leads and a slightly diphasic T wave over the left precordium with a rate of 75 per minute. When the patient stood, marked T-wave inversion appeared in all leads, with 1.0 mm. of RS-T segment depression at a rate of 120 per minute. Breathing a mixture of 6.7 per cent oxygen and 4.5 per cent

carbon dioxide produced a similar electrocardiographic picture after fifteen minutes, though the abnormality was slightly less marked (rate, 130 per minute). The patient could perform violently exerting tasks although he felt precordial pain after about five minutes. He was hospitalized and a duodenal ulcer was found. It healed uneventfully, but without alleviating his pain, which became more frequent and radiated to his neck and his left arm. It was felt that Buerger's disease, juvenile arteriosclerosis, and myocarditis could be excluded with reasonable certainty. The patient was finally placed in a "sanitorium for neurotics."

The author comments on the infrequency of cardiac pain with postural hypotension, the significance of the positive anoxemia test, and the possibility of true myocardial damage having gradually been produced by recurrent postural hypoxic episodes.

SAYEN.

Chini, V.: Clinical Aspects of the Associated Coronary and Cerebral Syndrome. Settim. Med. 35:443, 1947.

The author studied the frequency and types of various cerebral disturbances which may follow myocardial infarction. This clinical picture has been called "cerebral type of myocardial infarction"; the author refers to it as "associated coronary and cerebral syndrome."

Myocardial infarction may be followed by restlessness, mental confusion, stuper, loss of consciousness, coma, syncope, or epilepsy. The neurological signs may be preponderant, and occasionally mask the main symptoms of the disease.

The author reports thirty clinical cases which are divided into four groups:

Group 1 includes patients with coronary and cerebral episodes which are definitely independent. The only connecting link is the existence of arteriosolerosis in both the heart and the brain. Group 2 includes patients with a neurological syndrome which masks the main coronary disturbance. Group 3 includes patients with angina pectoris and episodes due to functional disturbances of the cerebral vessels. Group 4 includes patients having a coronary occlusion which was followed after a short period by cerebral disturbances.

The cerebral phenomena may be due to the following causes: embolism, thrombosis, hemorrhage, cerebral anoxemia caused by low blood pressure, shock, vascular reflexes, edema of the brain, or anatomical lesions existing before the coronary attack. More than one factor may be operative in these episodes.

Whenever a focal syndrome is present, either embolism or thrombosis should be considered as the cause. A sudden occurrence is in favor of embolism, while a gradual occurrence is more common in thrombosis. The absence of thromboendocarditis at necropsy is in favor of cerebral thrombosis.

LUISADA.

Barsoum, G. S., Kenawy, M. R. and El-Sheehy, A.: Absorption of Khellin and its Estimation in Blood and Tissues. J. Roy. Egyptian M. A. 30:312 (June), 1947.

The authors undertook to investigate the rate of the absorption of khellin after its administration by different channels and to determine the concentration which khellin reaches in the blood and tissues in animals and man. Khellin is extracted from blood or tissue by alcohol and chloroform. The concentration of this drug is determined by the modified colorimetric method of I. R. Fahmy or it is dissolved in Tyrode's solution and assayed by the biological method on the rectal cecum of the fowl (Anrep, Barsoum, Kenawy, and Misrahy 1946; Anrep, Kenawy, Barsoum, and Riad Fahmy, 1947) With concentrations of khellin in the blood varying between 1.0 and 200 micrograms per cubic centimeter, the plasma or serum contains about 10 to 20 per cent more khellin than the red blood cells. The authors found that khellin is readily given off by the corpuscles when they are exposed to serum or to Tyrode's solution containing no khellin; therefore, khellin in the red blood corpuscles is not pharmacologically wasted.

The experiments with intravenous injections of khellin were made on anesthetized dogs. The arterial blood pressure was recorded in the carotid artery and the injections were made slowly so as not to cause a fall of the blood pressure. After an intravenous injection the concentration of

khellin in the blood reaches a very high level for a short time. Within a few minutes the khellin concentration diminishes, and in about 30 to 40 minutes it reaches a steady level which is maintained for several hours. The rapid diminution of the khellin concentration in the circulating blood is due to its gradual and more or less uniform distribution among all the tissues of the body.

After intramuscular injection, khellin is extremely rapidly absorbed into the general circulation, and its concentration soon reaches a steady level, at which it is maintained for a long time. Maximal concentration reached after intravenous injection is much higher than after intramuscular injection of the same dose. Diminution of khellin in the circulating blood is not due to its elimination by the kidneys in an unchanged form. Since khellin remains in the circulation for a considerable time, administration of repeated doses should lead to an accumulation of the drug in the circulating blood. Animals receiving large doses of khellin showed, after repeated injections, a proportionately greater accumulation of khellin in their blood.

Human subjects were divided into two groups, the first comprising those who received their injection for the first time and the second, those who received daily injection for some days before the collection of the blood samples. The concentration of khellin in the blood was appreciably higher in those subjects who already had repeated injections of the drug.

Khellin is absorbed from the stomach, from the small intestine, and from the large intestine. The absorption from the stomach was studied in anesthetized dogs after complete separation of the pylorus from the duodenum. Absorption from the large intestine was studied only in man. The absorption of khellin from the stomach and especially from the intestine is very rapid. Absorption from the alimentary tract is, therefore, suitable for the maintenance of a high concentration of khellin in the blood, while intramuscular absorption is more suitable when it is desired to raise the concentration of khellin in a short time.

The disappearance of khellin from the tissues is extremely slow and is not related to any particular organ. Its concentration in the blood does not diminish more rapidly than in the tissues.

BELLET.

Küchmeister, H., and Taube, I.: Capillary Permeability in Malnutrition. Ärztl. Forsch. 1:278 (Sept. 25), 1947.

Protein content, number of erythrocytes, and volume of packed red cells in venous blood before and after application of an arm cuff at 40 mm. Hg for one-half hour were determined in eleven edematous patients (nine with hunger edema, and two with nephritis) and in fourteen normal subjects (method of Landis and associates: J. Clin. Investigation 2:717, 1932). From values so obtained, the loss of fluid and of protein in the venous blood after venostasis was calculated. Further, the colloid osmotic pressure of serum was determined in both samples of blood (method of Keys and Taylor: J. Biol. Chem. 109:47, 1935).

Patients with most marked edema showed the highest losses of fluid and protein (as much as 20.8 per cent and 1.53 per cent). There was, however, no relation between the total protein content in blood and the loss of both fluid and protein after stasis. The colloid osmotic pressure was not always dependent on the total protein content and sank more strongly than did the protein; in 55 per cent of the patients it decreased after stasis, as a result of the escape of proteins (especially of albumin). However, the values of protein content and of the colloid osmotic pressure found in the venous blood after stasis in edematous patients are either within or near normal limits. It must be assumed, therefore, that hunger edema is not only due to hypoproteinemia and to the consecutive fall in osmotic pressure, but also to changes in the capillary walls and in their function.

BRUMLIK.

Hirsch, S.: The Autonomy of the Coronary Circulation. Arch. d. mal. du coeur 40:433 (Nov. and Dec.), 1947.

The author redescribes the findings of his researches of the past seven years, during which time he has studied histologically the structures contained in the epicardial fat. He found specialized arterioles, the walls of which contained large, clear epitheliod cells and a sphincter-like

arrangement of smooth muscle fibers. The arrangement of the vessels here, especially in the deeper fat at the atrioventricular groove, suggested to him small arteriovenous anastomoses which he compared to glomus bodies. He described a rich network of nerve fibrils and ganglion cells. These anatomical features are offered as a mechanism by which the coronary irrigation is regulated from moment to moment to meet needs of the myocardium.

HECHT.

Vigiu, E., and Pilat, L.: On the Occurrence of an Accentuated First Heart Sound in Incomplete A-V Dissociation With Mitral Stenosis. Arch. d. mal. du coeur 40:446 (Nov. and Dec.), 1947.

The authors point out that previous explanations of the accentuation of the first heart sound at the apex demanded a short A-V conduction time by postulating the commencement of ventricular systole prior to the time when the mitral leaflets had floated into apposition, the "bruit de Cannon" then being produced by the addition to normal sounds of the sudden shock of mitral closure. A case is presented which the authors believe to be unusual because of the presence of prolonged A-V conduction time. In this instance they explain the accentuated sound by the prolonged period of ventricular filling which held and maintained the valve leaflets in the position necessary for the production of a loud sound. They hold that a "bruit de Cannon" in the presence of prolonged A-V conduction is prima facie evidence of mitral stenosis. Observations are supported and illustrated by simultaneous electrocardiogram, phonocardiogram, and venous and apex pulse tracings.

HECHT.

Burch, G., and Ray, C. T.: Vascular Responses in Man to Ligation of the Inferior Vena Cava. Arch. Int. Med. 80:587, (Nov.), 1947.

An analysis is presented of twelve female patients in whom the inferior vena cava was ligated for pelvic thrombophlebitis. After ligation of the inferior vena cava, the pressure in the dorsal pedal veins were markedly elevated (from 120 mm. to over 600 mm. of water). A gradual fall in venous pressure occurred with time, but only occasionally did it return to the maximal limits of normal. There was no relationship between the venous pressure and the degree of edema. Section of the lumbar sympathetic nerves did not influence the venous pressure. The paucity or even absence of edema in the lower extremities with considerable elevations in venous pressure made it necessary to re-evaluate the role of hydrostatic pressure in edema formation. Also interesting was the absence of abnormal dilation of the veins of the leg and the feet in the presence of pronounced venous hypertension. . In fact, several instances revealed veins of lesser caliber, indicating severe venous spasm. A definite venous hypertension in the superficial low abdominal veins indicated the development of venous collateral flow through these veins and in every instance, the direction of flow was cephalad instead of caudad. Clinical and physiologic observations failed to reveal any detrimental effect from ligation of the inferior vena cava. The circulatory adjustments were adequate, although not all the compensatory mechanisms were clearly understood.

BERNSTEIN.

Hirsch, S., and Zylberszac, S.: Cardiac Infarcts Induced by Excitation and Over-Exertion of Rats. Exper. Med. & Surg. 5:383 (Nov.), 1947.

The authors believed that the study of the role of the smallest blood vessels in the experimental production of heart muscle damage might require different and more delicate procedures than heretofore used. In searching for such procedures they found that under certain experimental conditions excitation and overexertion of rats produced definite pathologic changes in the heart muscle.

Excitation and overexertion of albino rats were induced by faradization in a specially constructed cage. When the rats were exposed to the faradization, their behavior was very characteristic. One group of animals did not try to avoid the faradization; they moved around in the

cage with signs of fright and excitement until they were unable to stand. The other group of rats developed a kind of protective posture; they crouched in one corner of the cage in such a position that the legs of only one side were in contact with the bottom of the cage. These rats were able to elude faradization for several minutes and were soon so well trained that they assumed their protective position as soon as they were transferred into the cage. Recovery after exhaustion occurred rapidly. All but two animals resumed a standing position a few minutes after the discontinuation of the faradization and started to take food. Eleven rats were exposed to faradization from one to six times.

Depending on the duration of the experiment and the frequency of faradization, increasingly severe changes were found in the heart muscle. The most common early findings were hyperemia of the capillaries and small veins, particularly in the papillary muscles. More striking were the changes of fibrocytes in the interfibrillary tissue of the muscle. These changes occurred as a rule during the first five days and were observed in four of the eleven rats after one to five exposures. In all instances where fibroblast formation and the development of young connective tissue was marked, fragments of disintegrated muscle fibers were found surrounded by connective tissue. The destroyed muscular tissue was eventually replaced by a scar tissue. This was observed in seven of the eleven animals on which this experiment was extended over a period of seven days or more, and after three to six exposures. In five of eleven rats, fully developed lesions were found. These lesions seemed to correspond closely to the histologic picture. In no instance was there any evidence of pathologic change in the branches of the coronary arteries.

BELLET.

Diamondstone, H., Braveman, L., and Baker, A.: Ventricular Tachycardia and Bilateral Amaurosis Produced by Quinine Poisoning. Arch. Int. Med. 80:763 (Dec.), 1947.

A case is reported of a white man who took a 10 Gm. dose of quinine sulfate, after which he developed ventricular tachycardia, acute coronary insufficiency with electrocardiographic changes, and bilateral amaurosis. Realizing the possibility that quinine produced these changes, this patient was treated as a case of quinine toxicity. The administration of vasodilators resulted in clinical improvement.

The authors believe that the toxic reaction to quinine, and possibly its isomer, quinidine, as demonstrated in this case, was due either to the direct action of the drug on the myocardium and/or to constriction of the coronary artery since constriction of the retinal arteries occurred.

BERNSTEIN.

Merkel, H.: The So-Called Primary Pulmonary Sclerosis. Beitr. z. path. Anat. u. z. allg. Path. 109:29 (Dec.), 1947.

Eight personal observations are reported and the literature dealing with primary pulmonary arteriosclerosis, pulmonary arteritis, chronic embolism of the pulmonary artery, idiopathic pulmonary arteriopathy, and pulmonary thromboarteritis is reviewed.

All subjects (47 to 76 years of age) were cyanotic and all showed considerable right ventricular hypertrophy. The most important clinical symptoms were cough and dyspnea. The correct diagnosis had not been established during life in any of the eight cases; mitral stenosis or myocardial degeneration was diagnosed wrongly instead. Variable arterioscleroic changes were found in the pulmonary arteries of all subjects; the small arteries and arterioles were involved more extensively than the medium-sized and large arteries. Primary pulmonary arteriosclerosis and pulmonary thromboendarteritis obliterans were the microscopic findings, each in four instances. No importance was ascribed to the coexistent pulmonary emphysema (all cases), chronic bronchitis (three instances), pleural adhesions (three instances), bronchial asthma (one instance).

The microscopic picture resembled that of systemic arteriosclerosis. However, no calcification in the large arteries and no fatty deposits or hyalinization of small arteries and arterioles were

observed. Aside from recent organization of emboli, no signs of inflammation were encountered. The changes in the elastica of the small arteries resembled the "hyperelastosis" of renal arteries. In four instances, endothelial desquamation and formation of fibrinoid thrombi with consecutive narrowing of the lumen were found in the pulmonary arterioles. The common denominator for this angiopathy is an isolated pulmonary arterial hypertension.

In some instances, despite the presence of excessive right ventricular hypertrophy, no changes in the pulmonary vessels were demonstrable. Since it is assumed that an increase in the peripheral resistance must have existed, it is postulated that pulmonary hypertension lacks morphologic manifestation.

BRUMLIK.

Borst, J. R., and Holleman, E. J. W.: Myocardial Infarction Resulting From Intravenous Administration of Hypertonic Solution of Sodium Chloride to Patients With Arteriosclerosis Obliterans of the Lower Extremities. Acta Med. Scandinav. 130:26, 1948.

Of eighteen patients with obliterating arteriosclerosis of the lower extremities, five were observed during an attack of myocardial infarction. In three of these, treatment with regular injection of hypertonic saline solution may have been directly responsible for the acute episode. In the first patient the attack commenced a few minutes after the infusion had been completed. In the second, an episode of severe vasospasm of the lower extremities occurred shortly after the end of such an infusion. An electrocardiogram taken ten days later revealed unmistakable evidence of subacute myocardial infarction, although no clinical symptoms had occurred at any time and previous electrocardiograms were normal. The third patient complained of increasing dyspnea and angina pectoris during the treatment, which necessitated its termination. Four days following the last treatment, the patient suffered an acute attack of myocardial infarction.

Infusions of hypertonic solution of sodium chloride increases cardiac output and the volume of circulating fluids. It is postulated that in subjects with latent disease of the coronary arteries, infusions of this kind may produce acute coronary insufficiency with resultant myocardial infarction.

HECHT.

Moe, T: A Case of Morgagni-Adams-Stokes Attacks Caused by Transient Recurrent Ventricular Fibrillation Without Apparent Organic Heart Disease. Acta Med. Scandinav. 130:416, 1948.

This report describes the case of a 38-year-old man who developed attacks of palpitation and who was admitted to the hospital with the typical clinical picture of long episodes of ventricular arrest. Two months after the onset of the earlier symptoms, electrocardiographic examination revealed that these attacks were initiated by a series of ventricular extrasystoles and consisted of long periods of ventricular fibrillation. Sixteen attacks were noted, lasting from 17.7 seconds to 2.5 minutes. Epinephrine was administered before the true nature of the attacks had been discovered. While the patient was under the influence of epinephrine, five spontaneous seizures occurred. Quinidine readily controlled the attacks. No evidence of organic heart disease could be demonstrated.

HECHT.

Borst, J. G. G.: The Maintenance of an Adequate Cardiac Output by the Regulation of the Urinary Excretion of Water and Sodium Chloride; an Essential Factor in the Genesis of Oedema. Acta Med. Scandinav. (Suppl.) 207:130 1948.

On the basis of a number of clinical observations supported by sodium and chloride balance studies, urea and creatinine clearance values, blood volume determinations, and observations on venous and arterial pressures, it is postulated that a close correlation exists between cardiac output and urinary excretion of water and sodium chloride. As soon as cardiac output declines

to subnormal levels, excretion of sodium chloride and water is reduced. The causes for the decline in output may be gastrointestinal hemorrhage, "shock," early congestive failure, forward failure of the circulation in general, hypoalbuminemia, and cirrhosis of the liver. Raising cardiac output by transfusion, and by digitalization in patients with heart failure and with untreated paroxysmal tachycardia (where an increased minute volume was postulated) resulted in marked retention of water and sodium. This led to an increase in the volume of extracellular fluid, a rise in venous pressure and cardiac output which, in turn, tended to correct the excretory deficiencies.

The author assumes that sodium retention in primarily based on excessive reabsorption of solutes by the renal tubules because little change was noted during the changes in sodium chloride excretion of the creatinine clearance values. The assumption that cardiac output is low in some and high in other syndromes examined was based on the clinical impression and arterial blood pressure determinations. The maintenance of an adequate cardiac output by a renal regulatory mechanism controlling the amount of circulating fluid and venous pressure is repeatedly emphasized.

HECHT.

Jönssen, G.: Visualization of the Coronary Arteries: Preliminary Report. Acta radiol. 29:536 (June), 1948.

In five of a series of patients in whom aortography was accomplished by rapid injection of contrast medium through a catheter passed up the radial artery into the ascending aorta (Radner, S: Acta radiol. 29:178, 1948), one or both coronary arteries were visualized. In four instances the tip of the catheter was near the semiluner valves and in one, a few centimeters higher. No attempt was made to study coronary artery anatomy in the roentgenograms which had been aimed at study of the thoracic arterial tree. There was no evidence of heart disturbance, and electrocardiograms before and after the procedure were unchanged. The roentgenograms of three patients are reproduced to show the coronary artery shadows. All three had been studied for patency of the ductus arteriosus. The safety of the procedure as compared with direct intraaortic injection of contrast medium is emphasized.

SAŸEN.

Hansson, C. J., and Jacobsson, E.: The Value of Roentgenography in the Diagnosing of Cardiac Disorder Following Rheumatic Fever. Acta radiol. 29:541, 1948.

All patients treated for rheumatic fever, or any other conditions commonly falling under this designation, at the Gothenburg Children's Hospital during the period 1922 through 1940 were submitted to a follow-up examination with a view to gaining some idea of the prognosis in this disease as it is seen in Sweden. The heart of each patient was submitted to a thorough physical examination, both under resting conditions and after exertion, and an electrocardiogram was also made in each case. Roentgen examination of the heart was then carried out.

The roentgenologist was told only that the patient in question had had a rheumatic infection, and, therefore, was not influenced during his studies by any findings that might have been made by physical examination. During the course of the investigation clinician and roentgenologist met for discussion and comparison of their findings in each individual case.

In 297 cases, (60.1 per cent) there was complete agreement between the clinical and roentgenographic findings. There was no agreement in 170 cases (39.9 per cent). It is also of interest to note that in no less than 150 cases the clinical examination revealed unequivocal evidence of organic heart disease, whereas the roentgen examination brought out nothing in this respect. In 387 cases (78.3 per cent), the roentgen examination was of no particular significance in the diagnosing of organic heart defects, since organic involvement could be established beyond all doubt by physical examination alone. In the remaining 107 cases (21.7 per cent), the roentgenogram was the decisive factor in the diagnosis.

BELLET.

Book Reviews

Diagnostico das Formas Anatomo-Clinicas da Cardite Reumatica. By E. Magalhães Gomes, M.D. Rio de Janeiro, 1947, Rodriguez and Co., 345 pages and 65 figures.

This book is a comprehensive study of rehumatic disease with special regard to rheumatic carditis. The disease is considered to be an infectious process with allergic reactions to the proteins of *Streptococcus hemolyticus.*

The diagnosis of the disease is studied with particular attention. Among the laboratory data, the Weltmann reaction is considered to be very accurate, a conclusion which should be accepted with reserve. The various possible complications of rheumatic disease are studied in detail. These include renal, pleuropulmonary, hepatic, thyroid, ocular, and neurological disturbances. The study of cardiac manifestations is completed by the description of clinical cases and the presentation of excellent electrocardiographic, phonocardiographic, and roentgenologic documentation.

This monograph should find its place in the library of all centers for the study of rheumatic fever.

A. Luisada, M.D.

La Pathogenie des Alterations Eléctrocardiografhiques de la Péricardite. By E. Coelho, M.D. Lisbon, 1947, Bertrand, Ltd., 74 pages and 58 figures.

This mongraph reports studies of the electrocardiograms in 138 cases of pericarditis. These include examples of uremic, tuberculous, purulent, and rheumatic types; hemopericardium and calcific and constrictive pericarditis are also studied.

Only six cases presented a normal electrocardiogram; in all others electrocardiographic changes were observed, at least in certain phases of the disease. The diagnostic value of the electrocardiogram was found to be high; in certain cases, fever and electrocardiographic changes were the only signs, and paracentesis of the pericardium confirmed the diagnosis. According to the author, there is no single type of electrocardiographic change and no typical evolution.

The electrocardiogram is of no help in making an etiological diagnosis. However, upward displacement of RS-T segment with high take-off of the T wave was found only in purulent and rheumatic pericarditis and never in tuberculous pericarditis. The deeply inverted T wave, encountered in certain cases of uremic pericarditis, is considered as a pre-existing change and sometimes the result of high potassium content of the blood.

In certain cases of associated rheumatic pericarditis and associated myocarditis, the electrocardiogram may contribute to the etiological diagnosis.

The evolution of the electrocardiogram varies in each type of pericarditis; the changes may persist indefinitely in cases of constrictive pericarditis. The most transient changes are observed in rheumatic pericarditis; in this type the changes may disappear within a few days unless constrictive pericarditis develops. In uremic pericarditis, the electrocardiographic changes are permanent. In purulent pericarditis, normalization of the tracing coincides with healing of the form, while persistence of the changes indicates constrictive evolution. Irritation of the pericardium due to hemorrhage causes changes which disappear after elimination or adsorption of the effusion. According to the author, complete evolution of the electrocardiographic changes, from the upward RS-T displacement to the inversion of the T wave in all leads, rarely is observed.

The author feels that neither myocardial anoxemia nor myocardial lesions explain the electrocardiographic alterations. These are due to irritation of the epicardium followed by bioelectric changes.

This extremely valuable monograph presents the protocols and documents of selected interesting cases and certainly will be quoted extensively in the future.

A. Luisada, M.D.

La Pression de la Arteria Pulmonar. By V. A. J. Alberti, M.D. Buenos Aires, 1948, El Ateneo, 170 pages and 40 figures.

A detailed study is made of the various experimental devices by which pulmonary artery pressure can be measured in animals. This is followed by several chapters discussing the effects

on pulmonary artery pressure of respiration, pulmonary embolism, pneumothorax, various reflexes, and various drugs. The last two chapters are devoted to the study of normal pulmonary pressure in man. Two methods are examined in particular: first, that of direct puncture of the artery through the chest wall, a technique devised by the author; and second, that of catheterization of the pulmonary artery.

The personal experience of the author with the various technical procedures is reported. For this reason and for the extensive bibliography, the book should prove to be valuable for students of the subject.

A. Luisada, M.D.

Doenças Cardio-Vasculares. By F. S. Laranja, M.D., and co-workers. Rio de Janeiro, 1948, Editora Cientifica, 733 pages and 215 figures.

This book is a volume in the collection of *Pathology and Therapeutics* by Struempell. The work of the old German clinician has been completed and revised by several Brazilian cardiologists under the direction of Dr. Laranja who has contributed most.

While the book suffers somewhat from its mixed origin, the knitting of old and new parts has been accomplished with skill. Many chapters are entirely new and among them is a valuable study of the cardiac lesions in Chagas' disease.

The book includes the following main divisions:

I. Etiological Factors of Cardiac Diseases.
II. Anatomical Changes of the Heart and Vessels.
III. Vascular Syndromes of the Heart.
IV. Functional Cardio-Vascular Disturbances and Treatment.

This scheme has the disadvantage of repetition. However, the concise form of the text partly compensates for it. Certain chapters seem out of proportion to others, but this can be explained by the importance that the diseases discussed in those chapters have in Brazil.

The documents presented are excellent; the sketches, clear. The binding of the book is first class while the paper varies from adequate to good.

A. Luisada, M.D.

Vascular Diseases in Clinical Practice. By Irving Sherwood Wright, M.D., Associate Professor of Clinical Medicine, Cornell University Medical College; Chief of Section on Vascular Diseases of the Department of Medicine, New York Hospital. Chicago, 1948, The Year Book Publishers, Inc., 514 pages and 104 figures. Price $7.50.

I know of no small book that offers such concise and practical information on a subject that is not too well taught even now in medical schools. The author is an outstanding authority on vascular diseases, and one who knows how to impart his knowledge to others. This reviewer has no criticism to make either as to the content of the text or the format. The author shows how any physician can diagnose and treat the diseases dealt with. After a chapter on classification and one on methods of study of the patient, individual diseases are discussed. It is to be hoped that the author will keep his book alive for many years by revisions as they may be indicated.

Wallace M. Yater, M.D.

Tonoscillography After Exercise. By Borje Ejrup, Med. Lic. Stockholm, 1948, Svenska Tryckeriaktiebolaget, 285 pages and 51 figures.

Dr. Ejrup presents a very complete monograph in an adequate English translation in which he discusses the instrument he demonstrated in 1943 for the automatic recording of peripheral arterial oscillations, and its use in intermittent claudication and a few related conditions.

The instrument which this author has devised is a very ingenious one for taking rapid, repeated oscillometric readings at regular intervals. The instrument accomplishes this automatically and makes a recording that does not have any subjective error.

The instrument automatically inflates (from tanked gas) a recording cuff to 50 mm. Hg and then inflates the proximal pressure cuff, gradually increasing the pressure as high as is needed,

and then releases the pressure in both cuffs. Another complete cycle is begun thirty seconds after the start of the first. The pressure cuff is connected to a lever which rises on a stationary drum and records the pressure at all times in a vertical line. Meanwhile the pulsations are recorded by horizontal deflections of the same needle. The drum moves 2.0 cm. at the close of each recording and is ready for another tracing. The result of this is a series of tracings from which both the systolic and diastolic blood pressures can be estimated and the amount of oscillations at the various tensions are a matter of permanent record. These are similar to the oscilometric readings which are usually taken, but they are recorded rapidly, frequently, and automatically. The machine is adaptable for either the one- or two-cuff method. Measurement of the oscillations can be made by having a standard amplification and by direct measurement of the swing, or by adjusting the maximal swing to a fixed amount and then by measuring the amplification required. While the latter method is preferable from theoretical considerations, it does introduce considerable subjective error and the necessity of a notation of the amplification, whereas the former is purely objective.

The fact that the tracings are taken fequently, rapidly, and automatically makes it possible to trace the degree of pulsations of the arteries immediately after exercise and to follow changes and recovery for as long as desired.

The author has very carefully checked so-called normal subjects and their responses to exercise. The normal subjects included postmen, dancers, football players, office workers, elderly subjects, and convalescents from nonrelated illnesses; none of the normal subjects showed evidence of vascular diseases. The author has shown that the normal reaction after standardized exercise is an increase in the systolic and diastolic blood pressures and in oscillations which lasts for a few minutes.

One cannot help but be impressed with the lengths to which Dr. Ejrup went to get a standardized procedure with many variables controlled and with the documentation of all subjects. Controls were checked with a complete physical examination, including palpation of all arteries, sedimentation rate, electrocardiograms before and after strenuous exercise, and fluoroscopy.

The differences obtained in the controls were a matter of degree and were reproducible in the same subject at different times. There was less variation after exercise than before. The explanation was offered that after exercise there was a measurement of the full capacity of the arterial system, whereas at rest the vessels might be in equilibrium at any point.

In patients with intermittent claudication there is a definite drop of blood pressure in the affected limb and a diminution of pulsations after exercise lasting from one and one-half to over twenty minutes. This premise was developed from thirty-four cases in which diagnoses of arteriosclerosis obliterans were confirmed by complete physical examination, including retinoscopic venous pressure, Decholin circulation time, electrocardiogram before and after hypoxemia and exercise, Nylin's function test, soft tissue x-ray films, complete blood count, sedimentation rate, cholesterol and total lipids, measurement of skin temperature before and after sympathetic block or tetraethylammonium chloride, and the reactive hyperemia test. In all the cases there were direct arteriographic x-ray studies which were correlated with the oscillograms.

Excellent quantitative correlation was noted between the degree of block and the localization of block in the arteriograms and the oscillograms. In 119 cases of definite proved intermittent claudication without arteriograms, there was comfirmatory evidence of blocks in the arteries, whereas in 455 cases with symptoms in the legs not believed to be of arterial origin the oscillograms were normal. Several cases were followed over several years with the exercise oscillograms paralleling the clinical course very closely.

There are also a few cases of Raynaud's phenomenon in which there were normal oscillograms before and after exercise. The author feels that this instrument is adequate for distinguishing organic disease from vasospastic disease, although he admits his series of vasospastics is still far too small. The reviewer believes that the evidence regarding this point is not conclusive.

There is an extremely interesting chapter on coarctation of the aorta. Twenty-six cases were studied after the resection of the stricture with end-to-end anastomosis of the aorta performed by Dr. Crafoord.

IRVING S. WRIGHT, M.D.

Elektrophysiologie. I. Band: Allgemeine Elektrophysiologie. II. Band: Spezielle Elektrophysiologie. By Hans Schaefer, M.D. Vienna, 1942, Lithoprinted by Edward Brothers, Inc., Ann Arbor, Mich., 1944, 44 pp. and 99 figures.

The author, the Director of the Department of Experimental Medicine of the once famous Kerckhoff Institute in Bad Nauhaim, Germany, has set himself a task that appears almost impossible of achievement. Without the usual staff of coeditors usually requisitioned for such undertakings, he ranges in these two volumes over the entire field of electrical properties of living tissues, exclusive of plants. Upward of twelve thousand references are cited covering 172 pages of fine print. This alone establishes the two volumes as an important guide book to anyone interested in fundamental approaches to medicine.

The book appeared in Germany during the war and to the reviewer's knowledge the original plates were soon destroyed. The only copies now available are those of the lithoprinted edition of the Edwards Brothers, published in 1944 by the Alien Property Custodian.

The first volume deals with general aspects of electrophysiology. It covers the passive electrical properties of living tissue, such as resistance, capacitance, polarization, and electrotonus. There follows a general discussion of the electrical response of tissue to external stimulation which includes a section on the excitability of individual tissues and organs in various species and quantitative data on Lapicque's rheobase and chronaxia. A chapter on the phenomenon of "local excitatory disturbance" (change in excitability during constant current application) leads to an extended discourse on the nature of action currents, resting currents, and injury currents (cell, skin, nerve, muscle). A chapter on transmission of excitation from organ to organ and one on the influence of poisons on the electrical properties of muscle and nerve complete the text of the first volume.

The second volume deals specifically with the electrophysiology of cardiac muscle, skeletal muscle and nerve, and with the electrical properties of sensory organs and of the central nervous system. A section on the electrophysiology of the skin and a chapter on the electrical phenomena of electrical fishes is appended.

Where the reviewer is able to critically evaluate the text, the occasional omission of pertinent references is unfortunate as the strength of the book is based to a large though by no means exclusive extent on the citation of the work of others and on its extensive reference section. It illustrates that the scope of the presentation begins to exceed the capacity of one single mind and that a joint authorship would perhaps have provided an even more comprehensive account. As an example may be cited the section on the electrophysiology of the heart muscle which serves well as an introductory guide to certain basic concepts. It cannot, however, be regarded as a final source book comparable, for instance, to the earlier and in scope much more limited volumes by Lewis and by Wenckebach and Winterberg. The author's preoccupation in this section with Schütz's and Schellong's debatable differential theory of the electrocardiogram serves to detract somewhat from an otherwise excellent presentation. It is gratifying to find that the ubiquitous role of the electrical responses of tissues as a primary phenomenon in general physiology is repeatedly emphasized throughout the book.

In spite of the slightly overponderous scientific German, the volumes represent an important, unique, and, with minor exceptions, successful distillation of the subject. The external appearance of the lithoprinted edition could be greatly improved.

H. H. Hecht, M.D.

Illustrative Electrocardiography, 3rd Edition. By Julius Burstein, M.D., and Nathan Bloom, M.D. New York, 1948, D. Appleton-Century Co., Inc., 309 pages, 99 plates, 23 figures. Price $6.00.

This book presents the rudiments of electrocardiography, phonocardiography, and radiology of the heart in a simple, concise manner and is so illustrated as to be understandable to the beginner in this field. Discussion of the material presented is brief. Controversial issues are avoided. A chapter on precordial and augmented leads is included. The authors, in nearly every instance, illustrate the subject discussed with an electrocardiogram showing all leads, rather than simply showing one lead, as is often done.

This is a well-arranged, elementary book designed for the beginner in this field.

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CARDIOVASCULAR REGISTRY OF PATHOLOGY

The first meeting of the Advisory Committee, with Dr. Wallace M. Yater as Chairman, was held in the Army Institute of Pathology, Washington, D. C., on Friday, Jan. 28, 1949. The entire Committee, Jesse E. Edwards, Jane Sands Robb, Joseph T. Roberts, and Helen B. Taussig, was present. General Raymond Dart, Director of the Institute, and Colonel James E. Ash, Scientific Director of the American Registry of Pathology, were also present.

This Cardiovascular Registry is sponsored by the American Heart Association for the following purposes:

1. The accumulation and maintenance of collections of pathologic materials and related case records.
2. The provision of consultation service for pathologists.
3. The preparation of teaching material in such forms as may be most readily and satisfactorily available for loan to qualified physicians, investigators, or students.
4. The establishment of facilities for the training of students and fellows in pathology.
5. To facilitate the accessibility of the materials in the Registry for students and qualified investigators who may be authorized to make definitive researches based on Registry material.

At its first meeting, the Committee voted to limit the collection of material to the following items:

1. Cardiovascular anomalies.
2. Subacute bacterial endocarditis.
3. "Collagen system diseases," particularly polyarteritis nodosa and disseminated lupus erythematosus.
4. Tumors of the heart and vascular system.

In addition, any interesting or unusual case is desired, particularly if a well-documented case report is available.

Cases may be submitted for consultation, but it is preferred that such cases be first examined by a local pathologist.

Special, simplified forms will be available shortly to facilitate the submission of clinical data.

All members are requested to cooperate so that the Cardiovascular Registry can be developed and can contribute to education and research in this field. Additional information can be obtained from the Director, Army Institute of Pathology, Washington 25, D. C., or from the American Heart Association.

VITAL STATISTICS

Figures on the causes of death in 1947 have been released by the National Office of Vital Statistics of the United States Public Health Service. Cardiovascular disease leads as the cause of death, with 626,176 fatalities in 1947 against 588,451 in 1946. The breakdown of the 1947 figure is as follows:

Diseases of the heart	460,580
Intracranial lesions of vascular origin	131,039
Acute rheumatic fever	1,024
Other diseases of the circulatory system	33,533
	626,176

Comparison of the total with deaths from other causes is as follows:

	1947	*1946*
Cardiovascular diseases	626,176	588,451
Cancer	189,811	182,005
Accidents	99,579	98,033
Nephritis	80,288	81,701
Pneumonia	61,836	62,324
Tuberculosis	48,061	50,911

1949 NATIONAL CAMPAIGN

Specific results of the 1949 Campaign cannot be reported until a later issue of the *Journal.* In general, satisfaction was felt with advance preparation for the drive, and the task of reaching the $5,000,000 goal was tackled with enthusiasm.

The theme of publicity and educational material was one of optimism and encouragement. This was echoed in the statement of President Truman and in the proclamations and statements of many of the State Governors. Newspapers, magazines, radio, and television all cooperated generously in carrying the message of hope rather than fear.

Radio Promotion

Opening day publicity was highlighted by an American Broadcasting Company radio network broadcast which heard addresses by Dr. Tinsley R. Harrison, President, and Harold E. Stassen, National Chairman. On the same date, Dr. Leonard A. Scheele, Surgeon General of the United States Public Health Service, spoke over the Mutual network.

Throughout the campaign period and just previous to it, numerous radio programs were devoted exclusively to the subject of heart disease or the campaign. These included an American Broadcasting Company network presentation of the history of the Association by Ted Malone; dramatic shows on all four networks dealing with rheumatic fever, high blood pressure, and other heart problems; a National Broadcasting Company round-table discussion; and talks by committee chairmen, including Maurice J. Tobin, United States Secretary of Labor, who is Chairman of the National Labor Committee.

Precampaign estimates were that almost without exception all sponsored network radio shows would devote commercial time to educational information or an appeal for funds. In addition, spot announcements were expected from nearly all of the 2,000 radio stations in the country; all but a few score requested kits and transcriptions for use.

Of major importance was the "Truth or Consequences" program conducted by Ralph Edwards and sponsored by Procter and Gamble. The "Whispering Woman" contest on this program was introduced on January 15.

Campaign Committees

Officially recognized campaign committees were organized in a great number of communities to conduct fund-raising and educational programs during the National Campaign in February. Most of these were under the sponsorship of existing local heart associations. Others represent potential local associations or chapters of state-wide associations.

The following is a partial list of cities where such campaigns were conducted. It does not include several hundred communities where committees were independently organized through joint enterprise of civic groups like the American Legion, Rotary, Lions, Kiwanis, and other public-spirited organizations:

Atlanta, Ga.
Austin, Texas
Baltimore, Md.
Binghamton, N. Y.
Birmingham, Ala.
Boston, Mass.
Bridgeport, Conn.
Buffalo, N. Y.
Charleston, W. Va.
Charlotte, N. C.
Chattanooga, Tenn.
Chicago, Ill.
Cleveland, Ohio
Columbia, S. C.
Columbus, Ohio
Cumberland, Md.
Dallas, Texas
Des Moines, Iowa
Detroit, Mich.
Fort Worth, Texas
Grand Rapids, Mich.
Hartford, Conn.
Houston, Texas
Indianapolis, Ind.
Jersey City, N. J.
Kansas City, Mo.
Memphis, Tenn.
Miami, Fla.
Milwaukee, Wis.
Minneapolis, Minn.
Nashville, Tenn.
Newark, N. J.
New Haven, Conn.
New Orleans, La.
New York, N. Y.
Peoria, Ill.
Philadelphia, Pa.
Portland, Ore.
Richmond, Va.
St. Louis, Mo.
St. Paul, Minn.
San Antonio, Texas
Seattle, Wash.
Springfield, Mass.
Syracuse, N. Y.
Trenton, N. J.
Tulsa, Okla.
Washington, D. C.
Wheeling, W. Va.
Wilmington, Del.
Winston-Salem, N. C.
Worcester, Mass.
Youngstown, Ohio

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The Third Inter-American Cardiological Congress

The Third Congress was held in Chicago, June 13-17, 1948, under the auspices of the Inter-American Society of Cardiology and the National Heart Associations of the Western Hemisphere. Its sponsors were the American Heart Association, the Chicago Heart Association, and the Illinois Heart Association. The host institution was Michael Reese Hospital. Members and official delegates came from thirty-six countries. At the inaugural session, they were officially welcomed by the Hon. Oscar R. Ewing, Federal Security Administrator and personal representative of the President of the United States; by Dr. Roland Cross, Director of the Illinois Department of Public Health and personal representative, of the Governor of the State of Illinois; by Dr. Herman Bundesen, President of the Chicago Board of Health and personal representative of the Mayor of the City of Chicago; by Dr. Arlie R. Barnes, President of the American Heart Association; by Dr. George K. Fenn, President of the Chicago Heart Association; by Dr. Harry A. Durkin, President of the Illinois Heart Association; by Mr. Grant Pick, President of the Michael Reese Hospital; and by the President of the Congress. Greetings extended on behalf of the delegates are included. Through the leadership and untiring efforts of its local committees and its officers, particularly its President, Dr. Louis N. Katz, the Congress was completely successful.

In recognition of the success and significance of this fine cooperative effort, which already is exercising an international influence, this issue of the American Heart Journal is being devoted to the business, social, and scientific proceedings of the Congress.

EXCERPTS FROM BUSINESS AND SOCIAL PROCEEDINGS

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GREETINGS FROM MEXICO EXTENDED BY DR. IGNACIO CHÁVEZ AT THE INAUGURAL SESSION

ONCE more those who study and practice cardiology have the pleasure of meeting together in this Continent. When the first Inter-American Congress was held in Mexico in 1944, its members included only a few Mexican cardiologists and a small group of our friends in the United States, Cuba, and Central America. However, our call was answered by some of the world's leading scientists, and sponsored by them, the Inter-American Society of Cardiology was born.

When we held the Second Congress about two years ago, we were not a small gathering but a magnificent and important group which included representatives of all of the cardiology societies on the American Continent and a select number of European cardiologists, who were the especially invited guests of Mexico. The International Council of Cardiology was established under its auspices; it will soon issue a call to cardiologists all over the world to meet in Europe in 1950.

As we celebrate our third reunion, it is a pleasure to review the ever increasing importance of our successive meetings. To the Heart Associations of Argentina, Brazil, Cuba, the United States, and Mexico, which took part in the last Congress, we have now added the recently organized Societies of Canada and Peru. We are grateful also for the increasing interest and enthusiasm displayed by our English-speaking colleagues, as evidenced by their support and by their

contributions to this Congress. Finally, we rejoice in having with us representatives from European Societies of Cardiology, as well as from the old universities of Europe. We men of science of the New World salute and extend fraternal greetings to our illustrious European colleagues who are with us.

The success of this Congress is already assured. Under the wise leadership of Dr. Katz and with the support given us by the outstanding sponsors, this Congress will surely mark an epoch in the development of our specialty. Its success should not be measured only in terms of the number of participants, which is larger than ever, nor by the importance of their contributions, which is indeed great. These yardsticks, important though they are, do not fully measure the significance of this Congress. Behind it all there is a spiritual meaning; something which is as valuable in human relations as the advances achieved in the scientific field. This spiritual value leads to mutual understanding between individuals and whole nations; it does away with the walls of isolationism and reinforces the bonds of mutual respect and friendship.

We are physicians and as such we are primarily concerned with the advances of medicine, but we are also members of the human race, and, furthermore, citizens of various countries which we love and honor. Pasteur has said, "Science knows no boundaries but the scientist has a fatherland." Therefore, each of us wishes to bring to his country well-earned prestige, respect, and honor.

This Congress offers the best opportunity to achieve these aims. We have brought here the best product of our efforts. Humble or rich, it constitutes a fine harvest which is dedicated to mankind's welfare. Fortunately, medicine is perhaps the only science whose objectives have not been perverted; the accomplishments of its investigators have not been turned into a means of destroying humanity.

The great city of Chicago had been selected to be our host because we realize the value of its contributions to the advance of medicine in the United States. If it were not for the splendid research work which is being done by the members of the Chicago Heart Association, the unique past contributions of Herrick and the present notable contributions of Katz would suffice to make Chicago the outstanding cardiac center that it is. Here, during this week, we shall witness the depth and richness of this country's scientific life as reflected by Chicago's medical institutions.

Fellow members: In the name of the Mexican delegation, I wish to thank the Michael Reese Hospital and its affiliated institutions for the generous hospitality accorded us. We pray for the success of this Congress and for mutual understanding between our countries through their men of science.

GREETINGS FROM ARGENTINA EXTENDED BY DR. PEDRO COSSIO AT THE INAUGURAL SESSION

IT IS an honor which far exceeds any merit of mine that I should have been chosen by the Directive Committee of the Third Inter-American Cardiological Congress to deliver a speech at this Inaugural Session and to represent South American cardiology, which is one of the oldest offshoots of the specialty of cardiology of this great and beautiful sister country.

In South America, cardiology made a somewhat precocious start as a specialized school of medical science in the first quarter of the present century; its pioneers were Raphael Bullrich and Gregorio Martinez of Argentina, Oswaldo de Oliveira of Brazil, and Julio Montes Pareja of Uruguay. Their inspiration emanated from the French School because directly or indirectly they were pupils of Henri Vaquex, who paid us a visit in 1924, and brought us up to date on the advantages of the use of ouabain in the treatment of heart failure.

The discoveries with regard to the mechanism of cardiac rhythm performed by Carl Wenckebach of Vienna and Sir James Mackenzie in conjunction with

Sir Thomas Lewis of London caused South American cardiology to turn its attention to these other Schools, and finally and definitely to align itself with that of the United States, when James B. Herrick of Chicago and Harold E. B. Pardee of New York established the clinical and electrocardiographic diagnosis of myocardial infarction.

Another important factor which guided South American cardiology toward its present course were the books, now classics, on diseases of the heart by Paul D. White and Samuel A. Levine. Both of these books had to be translated into Spanish to satisfy an insistent demand.

More important than all this, however, was the visit to South America in 1942 of Frank N. Wilson. Not only did he teach us, morning, noon, and night, everything necessary for the practice of rational and not merely empirical electrocardiography, but he succeeded in imparting his ideas and awakening a spirit of real investigation of the unknown; that is to say, he created a school of thought, with the result that we all esteem and venerate him as a veritable master mind.

The final link in the drawing together of the cardiological schools of North and South America was supplied by the Argentine Society of Cardiology, when it translated and adopted for the diagnosis of diseases of the heart the criteria and nomenclature prepared by the New York Heart Association, which had already been adopted by the American Heart Association. This action signifies that today throughout the whole of America the language of cardiology is one and the same, facilitating its comprehension and knowledge.

To finish with this brief summary, I wish to remember the names of the two forerunners. One was Francisco de Castro of Brazil, who published a noteworthy book in 1895 on the circulatory system, with profuse quotations from English and German literature, which at that time was almost unknown in South America. The other was Bernardo Houssay, an Argentine, who in 1930 sent one of his pupils to Western Reserve University to study the recording of cardiac sounds with Carl J. Wiggers, with the result that ever since then, Buenos Aires has made the greatest contribution toward the solution of this problem.

The natural consequence of all this is that the literature of cardiology which has held the first place during the last twenty years is that of this marvelous country. The desire to come here to study in your medical institutions becomes more fervent and widespread every day.

I myself came here for that purpose in 1936 and came back again in the year 1942 to deliver the Lewis Conner Lecture at the 18th Annual Scientific Meeting of the American Heart Association. Now I am here for the third time in my role of delegate to the Third Inter-American Cardiological Congress, that magnificent project of Ignacio Chávez of Mexico, which on the present occasion has been converted into a reality by Louis N. Katz, our present President.

The first time I took back with me to South America the knowledge I had acquired of something new, especially regarding methods of work. The second time I came here with my own humble personal experiences. Now I am the bearer of a message from the whole of South America to ask that the next Inter-American Cardiological Congress be held there. I trust that you will see fit to accept this invitation. In any event, I wish to express my thanks, no matter what the decision may be.

GREETINGS FROM EUROPE EXTENDED BY DR. GUSTAV NYLIN OF STOCKHOLM, SWEDEN, AT THE INAUGURAL SESSION

With the decline of the Greek civilization, the glorious heritage of Greek culture, art, and science passed to the younger, more vigorous Roman Empire. It was not merely that prominent Greek scientists and artists emigrated. It was rather that the sciences were reborn in the young Roman Empire and underwent unparalleled development. This new knowledge was later trans-

planted to France, and from there to the rest of the civilized world. The comparison is obvious when I, as a European physician, feel it a great privilege and pleasure to come to the American continent, which today is the foremost center of a tremendous expansion in culture and science. As a native of Sweden, I quite naturally see tangible proof of this in the fact that not less than 50 per cent of the Nobel Prize awards have been made to Americans in the years 1938 through 1947.

Cardiology as a field of research, like the cardiological associations, is of relatively recent origin, and the United States has played a major part in its development. But, though cardiology in its present form is a comparatively young science, the history of the study of the heart reaches back into antiquity. I need only mention how the heart was used as a symbol by the Egyptians and many other peoples, how it captured the imagination of primitive tribes, and how, through the centuries, it has been the subject of studies of a more or less scientific nature, according to the standards of research of different generations.

Only a few hundred years have passed since medicine and the whole range of human knowledge were one and indivisible. Today, in the light of the tremendous development in all fields, it is only natural that the science of medicine has been broken down into numerous component parts. Progress has been very rapid, particularly during the past few decades, and now more than ever before, we understand the importance of specialization. Admittedly, there is still resistance to the idea, even in the great land of opportunity, your own United States. Harvey Cushing, as we all know, had great difficulty in gaining recognition for his specialty. He, himself, tells the story in words that undoubtedly will become classical: "We all appear to be in the position of taking things away from one another—his problems, be he a practitioner. This has been so from the beginning of Medicine."

The cardiologists of the United States have played a great part, not least through the American Heart Association, in giving cardiology its rank as a specialty. The shape of modern cardiology has been molded by what we may call basic investigators, such as Harvey, Laennec, Einthoven, and innumerable other prominent physiologists, whose original purpose was not necessarily to contribute to the understanding of diseases of the heart. It was not until long after their observations that clinicians in different countries applied these basic scientific discoveries to cardiological problems. An army of indefatigable specialized workers have, each in his own way, helped to build up modern cardiology, of which clinical electrocardiography, cardiovascular roentgenology, and pathophysiological hemodynamics are the main supports. But we are still only at the beginning. Think, for example, of how Einthoven's great contribution has developed! In 1903 he published his most remarkable paper on electrocardiography, but it took more than a generation of painstaking research by cardiologists to evolve the empirical method whereby the physiological and the pathological in records of the electric potentials of the cardiac activity can be distinguished. A great many workers in different parts of this continent have produced a tremendous variety of results with the chest-lead technique, which admittedly are indispensable, but the significance of which we have not yet grasped. Frank Wilson's work is classic.

Roentgen's discovery was of enormous importance in giving us an objective view of the configuration and function of the heart, and its most recent result is the method of examining the heart and the vascular system with the help of contrast medium. Thanks to Laubry, Castellanos, Robb and Weiss, Châvez, and Dorbecker, among others, this diagnostic method has come to have decisive importance, particularly in the congenital heart anomalies.

In the field of hemodynamics, the basic research was done by Ludwig, Otto Frank, Krogh, Starling, Wiggers, Katz, Bernstein, Liljestrand, and U. von Euler,

who stimulated later clinical studies on circulation. From being limited to fairly simple bedside observations that were clinical in the strict sense of the term, clinical cardiological research has been transported into the laboratory, where it has been enriched by basic research in widely varied fields. Who would have dreamed, for instance, that atomic energy would come to have significance for the study of circulation? The radioactive isotopes have become the new microscope in medicine.

It might seem that the problems concerned are of theoretical interest only; but this is far from the case. Scientific discoveries must be the foundation upon which we base our actions, but at the same time the physician, and particularly the heart specialist, must understand and help the patient as a human being. We have all seen how diseases of the heart, blood vessels, and circulation have increased under the stress of modern life to the point where they are becoming a grave problem not only for the individual, but for society as a whole.

A Congress such as this provides an opportunity for personal exchange of laboratory findings and clinical experiences, which, in addition to adding to our knowledge, stimulates us to fresh endeavor.

As a European, I regret that we do not have with us today our Nestor, that great teacher, Laubry of Paris, nor that distinguished physician, Sir John Parkinson of London. It is gratifying, however, to note that many of the men who belong to the future in Europe have been able to join us. We have come together to exchange thoughts, to learn, and to observe, and the program gives promise that our high expectations will be more than fulfilled. I am convinced that all of our European friends, both those who are here today and those who were unable to come, will join me in extending heartfelt thanks to the hospitable United States and particularly to Dr. Louis Katz and his colleagues in the Third Inter-American Cardiological Congress.

PRESIDENTIAL ADDRESS BY DR. LOUIS N. KATZ

DISTINGUISHED guests, official delegates, members of the Congress, ladies and gentlemen: May I first of all express my own personal appreciation and that of my institution, the Michael Reese Hospital, for the confidence you placed in us in accepting Michael Reese Hospital as host of this Congress and in authorizing me to be its President. We consider this a special honor because this Congress is the first Inter-American Cardiological Congress to be held in the United States. We hope that you have been satisfied with the conduct of the Congress and I am sure that you will forgive us if it has failed to come up to your expectations in certain respects. The standards set at the First and Second Inter-American Cardiological Congresses in Mexico City by the Instituto Nacional de Cardiologiá de México, under the able leadership of its Director, Dr. Ignacio Chávez, were so high, you will admit, that it would be difficult, indeed, to approach them. We did our best.

I wish to take this occasion to thank for their untiring effort the many organizations and individuals who assisted me in this Congress. In particular, I wish to thank the local Committee, and especially the Chairman and Secretaries of the several Sub-Committees for their able and diligent participation. Above all, special appreciation must be given to the two persons to whom the major credit for the organization and arrangements of this Congress must go, namely, Mrs. Marie Cole de Pardo, Executive Secretary of the Congress, and my associate, Dr. Richard Langendorf, its Secretary-Treasurer. Both have worked hard and intelligently—yes, even "beyond the call of duty." A word of thanks should go also to the many volunteers who have given of their time. And finally, may I thank all of you for your patience and tolerance.

I cannot resist the temptation on this occasion to talk to you briefly about the future in the field of cardiovascular diseases as I see it. We have here with

us today some of the finest research talent from the Western Hemisphere, from Europe, and even from the far corners of the world, gathered to discuss work we have accomplished, to exchange ideas, to stimulate one another so that we may go back to our clinics, our hospitals, our medical schools, and our laboratories to continue the good work done in the past. This is truly an international gathering without the turmoil and discord that is found in international political meetings because we are all working through our discipline, cardiovascular science and medicine, for a common goal, the benefit of man. As is true of most scientific gatherings, we are imbued with the merits of our worthy cause and have little time for the squabbles that plague other international gatherings. This is good.

It is remarkable also that we have in our midst eminent internists, surgeons, roentgenologists, pathologists, physiologists, pharmacologists, biochemists, biophysicists, bacteriologists, and other specialists. I think this represents a new fruitful departure from the traditional separation of these disciplines in the past. Here, we men and women of varying scientific and medical backgrounds are gathered together to think through the problems of diseases affecting one of the major organ systems of the body: diseases which in a country like the United States are the leading causes of disability and death, far above all others. As we review what has been accomplished in the last quarter of a century, what has happened in the two years since the Second Inter-American Cardiological Congress, and what is being presented at this Congress, we have great cause for pride in our accomplishments.

It is interesting that the traditions of Europe remain, that European influence has spread to the Middle East, to the Far East, to Oceana, and to both North and Latin America. We can see how there has grown up in the Western Hemisphere a magnificent discipline with many minds and many institutions devoted to cardiovascular diseases. But to me, it is far more significant to have watched the recent tremendous growth of the discipline of the study of the circulation in Latin America; the amazing institute headed by Dr. Alberto Taquini in Buenos Aires and the finest of all institutes in our field, located in Mexico City, the National Cardiological Institute of Mexico, with its affiliated departments of fundamental medical sciences, with its magnificent complement of distinguished physicians and investigators, all integrated by my good friend, that able leader, the founder of the Inter-American Society of Cardiology and its Permanent Honorary President, Dr. Ignacio Chávez. This institution in Mexico City and its personnel have not been excelled in the past. Through this institution, Mexico has set a standard which should be striven for in other parts of the world.

It seems to me that the approach of this Mexican institution is the one required to attack and conquer the diseases of the heart and blood vessels more effectively and more rapidly than has hitherto been possible. What is more exciting and productive than the gathering together of experts of various backgrounds dedicated to the diagnosis, care, and prevention of this important group of diseases? The constant interplay of a coordinated team is bound to lead to important positive discoveries, as those of us who were in Mexico had the good fortune to witness. I was personally delighted that we had the opportunity Tuesday night to see a film of this institution presented by Dr. Chávez. I insist that the future of cardiology, in its broadest terms, is dependent upon the creation of many such institutions throughout the world. This, together with the meeting from time to time of physicians and scientists of all countries interested in cardiology, is the hope of the future.

It is obvious, however, that it is not enough to have magnificent institutes and splendid staffs; we must define our objectives more precisely. What is it that we are aiming for? It is obvious that we are trying to improve our diagnostic skills so that we may be better able to recognize diseases of the circulation

earlier and to define the varieties more precisely. It is obvious that we must know the geographic distribution of these diseases and their natural history so that we may, throughout the world, be better prepared to recognize and cope with them, and be better equipped to prognosticate the future of patients afflicted with these diseases. But these are not ends in themselves; we must strive to improve the treatment of the diseases of the heart and blood vessels, to counteract heart failure and circulatory failure, to make it less empiric and more scientific, and to establish precisely what can be hoped for from surgery of the heart and blood vessels. While we must not discount authority and the accumulated knowledge of the past, we must not, on the other hand, revert to the stagnant era of uncritical dogmatism and scholasticism which followed Galen for a long time.

The progress in diagnosis, prognosis, and management has been gratifying, indeed. It would be pointless for me to attempt to narrate the important discoveries which have been made. You are all as keenly aware of them as I am. However, it might be worth while to pause a moment and compare the attitude to diseases of the circulation now and thirty years ago, when I first became interested in the subject. I can recall vividly how unsatisfactory our knowledge was at that time. Diseases of the heart and blood vessels were considered necessary evils which were inflicted upon mankind and which had to be tolerated. The highest aim in the field of cardiovascular diseases seemed to be to see how precisely during life one could make the necropsy diagnosis. It was a period of therapeutic nihilism. There was little effort, so it seemed to me, to reverse the process. Today things are different. Many forms of heart disease can be arrested, some can be reversed, and some are even cured. There is no question but that the result of our work is the substitution of the new psychology of hope for the old psychology of fear.

As a by-product of this positive approach, one important development has occurred within the last decade, namely, cooperative study involving many people and many institutions. For example, this was the case in the evaluation of quinidine derivatives under the leadership of Dr. Paul D. White. This has been the case in the investigation, under the leadership of Dr. Irving Wright, of the value of dicumarol in recent myocardial infarction. I can see great promise of real accomplishment by such cooperative studies in the future, in which the individual physician and investigator and the individual institution is able to merge the competitive spirit in an integrated cooperative study, because it is recognized that the information and benefits to be derived are far greater than could be achieved by each one working independently.

The aim of medicine is broader than the endeavor to diagnose, prognosticate, and manage disease. Far more important, as we all know, is prevention. There is a vast area of study still remaining in preventing cardiovascular disease, despite the considerable knowledge that has accumulated on this subject. More and more of our efforts, I believe, should be directed toward this goal.

Finally, we should stop and pause and ask ourselves: What are the major basic problems in our field? I am sure that you will unanimously agree that based on their importance, there are three fundamental problems at the present time, the solution of which will be epoch making.

First, what is rheumatic fever? What is the organism which is responsible for it? Is it a virus? Is allergy involved? What is the role of the collagenous tissue? Is rheumatic fever a response by the host of a set kind to a single outside agent, or are a multiple of agents involved, all leading to a similar response?

Second, why high blood pressure? Despite the brilliant work of the Buenos Aires school of Drs. Braun-Menéndez, Taquini, Fasciolo, and others, under the able leadership of Dr. Houssay, despite the fundamental work of Dr. Goldblatt,

the question still remains: What precisely is the role of the kidney in the pathogenesis of this disease? Is hypertension neurogenic, psychosomatic, or is it due to some hitherto unresolved hormonal disturbance? What is the nature of the primary involvement of the blood vessels? What makes hypertension become fixed? What is the role of habitat and environment and diet?

Third, what is the cause of hardening of the arteries? Surely, it is not simply aging. Aging is an expression we use too often to hide our ignorance behind. What is the role of the nourishment of the blood vessel wall in its genesis? What is the part played by the lipids and cholesterol? How far does diet aid in its development? Is it a long-term effect of some neurogenic or hormonal disturbance?

Rheumatic fever and rheumatic heart disease, essential hypertension, and atherosclerosis are the principal causes of heart disease. Real progress in the eradication, in the alleviation, in the management, and in the prevention of these diseases must await answers to the pathogenesis of these major disabilities. These are difficult problems to solve. They demand the full-time cooperative energy of the ablest among us, clinician and investigator alike. They demand the full-time activity of our best intelligence. We need the services of many teams consisting both of mature and of promising young men to concentrate on these problems, men who will devote their lives to a concerted attack, men who will not be discouraged if for years they have little or nothing to report. Men willing to dedicate their lives to the study of these major problems should be assured an adequate income, should have adequate facilities for their research, should be provided with sufficient technicians and experts in allied fields so that they may follow their ideas unrestrained wheresoever they may lead them. This is the lack at present as I see it. This is the need that must be met in the future. Should this need be met in generous fashion, I am sure that the answers to the major problems will be forthcoming, perhaps sooner than we imagine, perhaps even in the life-time of the younger ones among us. Then we shall be repaid manifold for our efforts and we shall have realized to the full the promise held forth in this Congress which we have created.

Thank you.

THANATOPHAGIA, DANGERS OF DINING

DR. HOWARD B. SPRAGUE

AN ADDRESS MADE AT THE BANQUET OF THE CONGRESS

I APPRECIATE the honor of being invited to address you even though I realize that I am only a substitute in place of your original entertainer. The appreciation of such an honor by an after-dinner speaker, however, is always diluted by the realization that he is not expected to say anything of importance. That, however, is proper, since at a medical conference of cardiologists the evening banquet should be the diastolic, or resting, phase of the meeting.

I also apologize to our Latin-American members for speaking to you in my native language. I am reminded of an incident of the war in which a naval officer told of meeting in the wardroom of a foreign allied vessel a group of officers representing seven nations. "Fortunately," he said, "we were all very fine linguists, that is, we all spoke English."

When Dr. Katz got in touch with me a week or so ago to ask me to give this talk, he used an agent more terrible than the atom bomb, that is, the long-distance telephone, which permits the victim no time for thought or excuses, and I found it easier to say "yes." He told me that I could talk on any subject, and so I have made up a subject for you. I contrived the word, Thanatophagia, from the Greek Thanatos, meaning "death," and phagia, "eating." Thus, we have death-eating, or the Dangers of Dining. It should remind us all of the

Ninth Century Arabian proverb that "the two greatest hazards of an aging man are a good cook and a young wife."

I shall not discuss all the dangers of dining. I well remember the days when Richard Cabot used to caution us, as students, that at the onset of any disease, the patient, or some member of his family, could always remember something that he had eaten that must have been responsible. There are, of course, the dangers of gorging and of the "acute indigestion" of the pre-Herrick days. On one occasion I had the opportunity of saving the life of a friend of mine who, after a bevy of Martinis, tried to swallow too large a piece of steak.

But concerning that of which I now speak, and here demonstrate as an apparently harmless white powder in this bottle, I feel like one of the Borgias. This is a substance which is contained in the bodies of all of us here; one-half of it is in our brains. Each of us possesses within him about 50 grams, which is worth, at retail, about $3.75. But for the past thirty-five years it has steadily gained in prominence as the villain in our daily lives. I refer, of course, to cholesterol. That not all of you are terrified of it is shown by your consumption of this meal, which has probably provided you with the average daily intake of one-third of a gram. Like women, it is something difficult to live with or without.

I feel that I am invading the field of my friends, Louis Katz and George Herrmann, in discussing cholesterol and coronary disease, but I believe it is legal for me to do so since even we at the Massachusetts General Hospital are working on the subject, though with a rather different approach. We are trying to find out what kinds of people acquire the disease, rather than what kinds of animals can be made to develop it.

The first unhappy beast to succumb to atherosclerosis by heavy, prolonged dosage with cholesterol was the rabbit, and he can quite readily be made to develop it. On the other hand, carnivorous animals do not develop it naturally; Fox, from his fascinating work at the Philadelphia Zoo, states that no wild rodent ever gets atherosclerosis. Omnivorous animals, if sufficiently debauched by investigators, will acquire it. Katz and Herrmann can accelerate it in chickens with high-cholesterol diets, but chickens normally develop it with age. Steiner and his associates have finally produced it in dogs by a combination of cholesterol feeding and a disturbance of thyroid function with thiouracil.

As for man, atherosclerosis, as Dock points out, is rarely seen in people with diets high in whole cereals, beans, and vegetable oils, whereas it is common only in those with diets rich in animal fats but poor in animal viscera, and especially in diets with much milk, fat, and egg yolk.

Arteriosclerosis, implying largely a medial affair, a picture of fibrosis, desiccation, and calcification, comes normally in chickens, eagles, elderly cows, and gourmandizing, irregularly eating carnivora; but Fox has shown that old, male parrots have atheromatous possibilities in their vessels beyond those of any mammal except man. The parrot is probably also the only other creature which would be invited to give an after-dinner speech.

Commander P. E. Steiner of our Naval Reserve Medical Corps contributed very suggestive data to our knowledge of this subject in his autopsy studies during the war of undernourished native Okinawans. He found that they did not suffer from coronary disease, but demonstrated that they had long, capacious, tortuous, large intestines like herbivorous animals. They eat predominantly a vegetable diet of sweet potatoes and rice; a diet low in fat and protein and with the protein mainly from soybean. They have little meat and milk. From this demonstration we might take a more positive stand about such a diet than did Dr. Hutchinson when he said that, in general, a vegetarian diet was harmless, but tended "to fill a man with wind and self-righteousness."

Our own Dr. Chávez has shown, for example, that hypertension, angina pectoris, and coronary thrombosis were uncommon in Mexican Indians in spite of

the fact that arteriosclerosis was as common as in white subjects. Kuczinski found that Kirgiz nomads with high-fat diets had a marked incidence of atherosclerosis, while their contemporaries in the towns, living on a mixed diet, did not.

It is of interest that Eskimos on high-meat diets have low blood pressures, relatively low blood cholesterols, and high basal metabolic rates. Those of you who have seen Commander MacMillan's motion pictures will recall their eating habits, especially their netting, skinning, and consuming raw the entire bodies of small auks which they dip out of the air.

The whole subject of blood cholesterol is very confusing, however. Pyknic individuals are said to have higher cholesterol levels than asthenic individuals, which complicates the situation in relation to normal standards since our work so far seems to confirm the tendency to mesomorphy in premature coronary disease in men. Katz has recently noted that his chickens on a low-fat diet had a higher blood cholesterol than those on a high-fat diet. This raises the questions involved in the reaction to starvation and all the complexities of endogenous cholesterol.

I wish to touch on one other paradox, that of the teeth. Wild animals usually die because they lose their teeth, and suffering from malnutrition, become easy victims of the elements or their enemies. This is negative thanatophagia. Men, on the other hand, seem to live longest on diets which are bad for their teeth. New Zealanders, with the longest life expectancy of all, have much dental trouble.

This reminds us of McCay's famous rats. He found that diets satisfactory in food elements, but so low in calories as greatly to retard maturity in the rat, resulted in pronounced lengthening of life. Well-fed, handsome young rats succumbed earlier in life. It makes one wonder about our own pediatric concepts.

Perhaps we can, for a moment, defend the egg. For the sake of our Latin-American friends here tonight we may remind ourselves that Columbus first made the egg stand up for itself, and, from a practical point of view, in the ordinary man, cholesterol, as such, may be less important than fat. I refer, of course, to the recent presentation of Moreton in relation to the physical state of the plasma lipids. It is his contention that the explosive delivery into the blood stream of large fat particles coincident with repeated heavy fat meals provides the mechanical insult to the coronary intima similar to what occurs in the persistent hyperlipemic states, such as diabetes, which are notorious precursors of atherosclerosis.

What may be some of our inconclusive conclusions at this point? First, the effects of the ingestion of fats and cholesterol are but partial factors in the equation. True, we may be dealing with essentially a quantitative problem in various experimental animals, but this does not apply clinically to man. That is, there are different kinds of men and different reactions to diet. There may well be herbivorously constructed men, like rabbits, and carnivorously constructed men. Perhaps we would find out more about coronary disease by studying the types of large bowel possessed by men than by recording their blood cholesterol levels.

Nor does this explain woman's relative freedom from coronary disease. I dare not say here that such conclusion is well founded, but one might imagine that woman was essentially a predatory carnivorous animal—I did not say "rodent."

It may also be lamentably suggested from racial studies that the price of freedom from coronary disease may be cirrhosis of the liver, since this is common in peoples relatively immune to atherosclerotic tendencies.

I believe, however, that men should live on diets very low in fats and cholesterol if they come from "coronary" families, are predominantly mesomorphic in body type, and especially if they have seriously encroached upon their normal fat deposit areas.

It was of interest to me two years ago to examine, at my own request, the oldest living graduate of Harvard College. He will be 103 years of age next month. He is a healthy, spare individual with normal physical findings except for visual and hearing defects. His electrocardiogram is normal. I hesitate to mention this in the presence of Dr. Wilson, but I recorded CF precordial leads rather than V leads. I recently asked his wife about his dietary habits. This is her reply. "As to Mr. Adams' diet, he has an excellent appetite and can eat anything except pork. He eats any strip of fat on meat. He never salts his food at the table as it is well seasoned in the kitchen. He has top milk on cereal, not heavy cream. All his life his breakfasts have been cereal, boiled egg, and coffee, but no bread. In his younger days when he was teaching he ate two boiled eggs every morning. His favorite dessert is apple pie, which he does not have very often, and ice cream, which he has once a week. He is fond of sweets and every day has soft chocolate candies after dinner. He does not care for supper, but always takes a glass of sherry or muscatel with cookies just before retiring."

You will note that this man has eaten eggs every day for one hundred years. I have estimated that he has consumed about 56,000 eggs without acquiring lethal cholesterosis. This is very reassuring to us egg eaters.

In deferring the fatal influence of cholesterol and other factors in thanatophagia, I am reminded of what Marcel Proust once said, "Nature hardly seems capable of giving us any but quite short illnesses, but Medicine has annexed to itself the art of prolonging them."

With this in mind, I decided that I would close with a medical interpretation of a famous quatrain of Omar which may perhaps be used as a prescription for longevity.

"A book of verses underneath a bough"

This refers to the relaxations of the literary life. The "bough" might be, in the winter, in one of our delightful Latin-American countries. In the summer, so far as I am concerned, it could be in Maine.

"A jug of wine, a loaf of bread"

You will note that the jug of wine comes first. I am sorry that Dr. Stroud is not here to comment on this. The loaf of bread is low in cholesterol, can be low in sodium, but should have added vitamins.

"And thou beside me, singing in the wilderness."

The "thou" in this case should be an affectionate, but not too demanding wife, preferably your own. The soothing influence of song is obvious.

"And thou beside me, singing in the wilderness,
Ah, Wilderness were paradise enow."

ANNOUNCEMENTS

DR. ANTONIO BATTRO

At the beginning of the Plenary Session, the President made the following simple statement:

"Dr. Antonio Battro, Professor of Clinical Medicine at the University of Buenos Aires, one of our active members, died unexpectedly of a coronary attack. We shall rise for one minute of silence in his memory."

THE FIRST INTERNATIONAL CARDIOLOGICAL CONGRESS

In the name of the International Council of Cardiology, Dr. Paul D. White made this announcement:

"It has been agreed by the International Council of Cardiology to hold the First International Cardiological Congress in July, 1950, in Paris under the Chairmanship of Professor Charles Laubry, who has appointed a local committee to help him and who will receive advice from the other members of the International Council of Cardiology."

Original Communications

ON THE POSSIBILITY OF CONSTRUCTING AN EINTHOVEN TRIANGLE FOR A GIVEN SUBJECT

Frank N. Wilson, M.D., J. Marion Bryant, M.D., and
Franklin D. Johnston, M.D.
Ann Arbor, Mich.

INTRODUCTION

For more than a third of a century students of electrocardiography have struggled with the concepts that underlie the equilateral triangle of Einthoven, Fahr, and De Waart, and have continuously debated the validity of the assumptions it involves. During this long period numerous investigators have attempted to settle these disputes by generating an electric field of the appropriate kind in a human cadaver, or in some sort of model, and comparing the experimental results with the theoretical predictions. The more important of these studies have been reviewed in a recent article from this laboratory,[1] and the results of a cadaver experiment, of the kind in question, performed here a number of years ago have now been published[2] in connection with a discussion of the possibility of converting the Einthoven triangle into an equilateral tetrahedron.

It is our present purpose to present and discuss the results of some experiments of this same general sort in which the cadaver, or model, has been replaced by the body of a normal human subject. This substitution offers some very obvious advantages and it involves no very great flight of the imagination. We have wondered why we did not attempt it long ago and from what source came the suggestion that led us finally to make it. The train of thought concerned cannot now be traced to its origin with any certainty, but it may well have been the result of a discussion, in the autumn of 1944, when one of us appealed to Dr. Kenneth S. Cole and Dr. Alvin M. Weinberg for advice as to the best way of measuring the magnitude of the potential variations of a central terminal connected to the limb electrodes through equal resistances. Dr. Cole expressed, on this occasion, some dissatisfaction with the means previously employed for this purpose and intimated that a more direct approach to the problem was preferable and ought to be feasible. Apparently, his first reaction was that it might be

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possible to obtain the desired information by mapping the isopotential lines of the cardiac field on the surface of the trunk. After further consideration, however, he remarked that the problem "might be reversed" by introducing a three-phase alternating current into the body by way of the limb electrodes and finding on the anterior and posterior surfaces of the chest the points at the same potential as the node formed by the three phases in Y or star connection. Some months later, preparations for carrying out this experiment were made but they were never completed, partly because it was found that when two limb electrodes were connected to a source of low frequency alternating current and also to a central terminal, through equal resistances, the location of the line on the body surface corresponding in potential to this terminal was determined chiefly by the relative magnitude of the two "contact" or "skin" resistances involved. The question then arose as to whether the measurement and equalization of these resistances (by the method of equalizing the resistances in the limb leads described by Einthoven, Bergansius, and Bijtel[3]) would not defeat the main purpose of the investigation. Dr. Cole suggested later that we connect the current source to two of the limb electrodes, using each of the three pairs in turn, and plot the points at the same potential as the third. The results of a few experiments of this kind are described in a later section of this paper.

The experiments with which we are at present mainly concerned were begun in September, 1946. We have frequently interrupted them for the purpose of analyzing the results of those already done and of studying the theoretical questions and the technical problems encountered. To a very large extent they have been of an unsystematic, preliminary, and exploratory kind. We are far from satisfied with the data collected thus far and are in the process of trying to perfect the technical procedures required to the point where the variation of the results on repetition of a given experiment will be negligible for our purpose. For this reason, the conclusions suggested by the observations available at this time must be regarded as subject to future revision.

When we began our investigations we were not aware of the work of Burger and Van Milaan[4] of Utrecht, who for several years have been studying electric fields generated in a model of the human body which they have built. Since we have become familiar with their publications we have been considerably influenced by their ideas, and particularly by their elegant method of constructing a triangle which summarizes all the information, concerning the nature of the electrical field in their model, obtainable by measuring the potential differences between electrodes corresponding in location to the limb electrodes used in clinical electrocardiography.

In our earliest experiments, one set of three electrodes was placed on the extremities in the usual way. Three electrodes were also placed on the anterior surface of the body, one just above the symphysis pubis and the other two near the junctions of the arms with the trunk. Three additional electrodes were put on the back and these were located as nearly as possible directly behind the corresponding electrodes of the anterior set. From these nine electrodes the following leads were taken: (1) the usual limb leads (I, II, and III); (2) corresponding leads from the anterior electrodes (IA, IIA, and IIIA); (3) the same

leads from the posterior electrodes (IP, IIP, and IIIP); and (4) a lead from each of the anterior electrodes to the corresponding posterior electrode (RR, LL, and FF).

It should be pointed out that whereas the exact locations of the limb electrodes are a matter of no importance, the positions of the electrodes on the trunk must be determined with considerable precision if consistent results are to be obtained in experiments on different subjects. With this in mind the following plan for placing these electrodes was adopted. Each of the upper anterior electrodes was put in the area bounded laterally by the palpable coracoid process of the scapula and above by the inferior margin of the clavicle. The corresponding posterior electrode was then placed directly behind it and immediately below the scapular spine. The inferior posterior electrode was put in the midline on the lower part of the coccyx, and the corresponding anterior electrode straight in front of it, on the midline and just above the pubic symphysis. Even though considerable care was used in the placement of these electrodes, it seems not unlikely, when we consider that human chests vary greatly in size and shape, that the personal equation involved in deciding upon their exact positions sometimes had an effect upon the relative magnitudes of the deflections in the leads requiring their use.

The electrocardiograms of normal subjects which have been taken by this system of nine leads are all much like that reproduced in Fig. 1. It will be noted that the deflections in Leads RR, LL, and FF are strikingly similar in general outline but very different in magnitude. Those of Lead LL are largest, and those of Lead FF smallest. This is true of all of our records of this kind. In taking these sagittal leads the galvanometer connections were made in such a way that relative positivity of the posterior electrode produced an upward deflection in the completed record. The relations between the nine leads from the electrodes on the front and back of the trunk are expressed by the equations that follow. In these equations the symbols *IA*, *IIP*, *RR*, etc., may be regarded as representing the leads for which they stand, considered as vectors which are to be added vectorially according to the parallelogram law, or as representing the deflections in these leads, which are to be added algebraically.

$$
\begin{array}{ll}
(1) & IP + RR = IA + LL \\
(2) & IIP + RR = IIA + FF \\
(3) & IIIP + LL = IIIA + FF \\
(4) & IP + IIIP = IIP \\
(5) & IA + IIIA = IIA
\end{array}
$$

In the experiments in which an artificial field was established in the trunk we employed a vacuum-tube beat-frequency oscillator to generate a current alternating 25 times per second. This current was introduced into the chest by way of two small circular electrodes and was maintained constant by means of a sensitive rectifier-type milliammeter. The diameter of the electrodes, the distance between their centers, and the magnitude of the current passed into the body have varied in different experiments. No systematic study of the effects of these variations has been made, but in general, the potential differences between

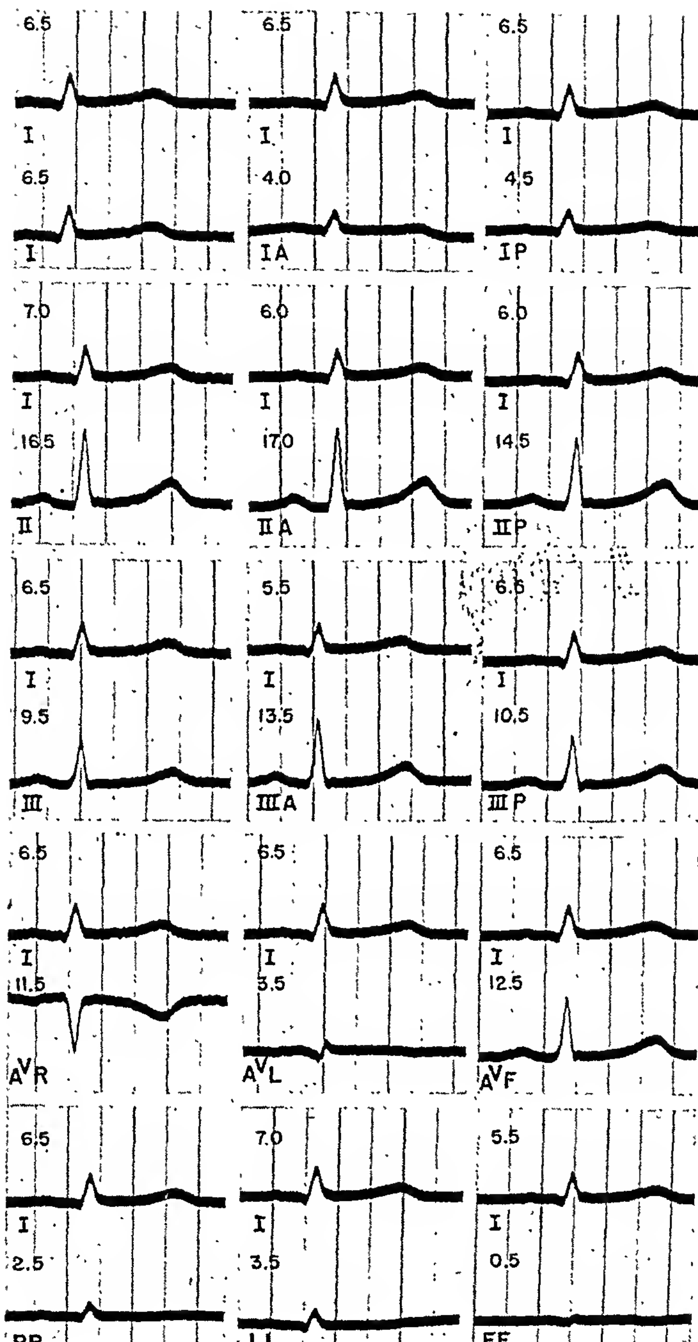


Fig. 1.—Experiment 5, *a*. Electrocardiogram of a normal subject showing the standard limb leads (I, II, and III), the corresponding anterior (IA, IIA, and IIIA), and posterior leads (IP, IIP, and IIIP), the augmented unipolar leads (aV_R, aV_L, and aV_F), and the sagittal leads (RR, LL, and FF).

the extremities have been roughly proportional to the product of the current and the distance between the input electrodes. It will be convenient to refer to this product as the electrical moment.

At the beginning of an experiment a point on the chest was selected and the centers of the input electrodes were placed on a line drawn through this point in such a way as to make the distances of their centers from it equal. In the case of a given subject the electric field established in the trunk by connecting these electrodes to the oscillator is then adequately defined by giving the location of the point mentioned, the distance between the centers of the electrodes, the magnitude and character of the current, and the angle between the line specified and the horizontal. After the first two or three experiments the location and manipulation of the input electrodes was greatly simplified by fastening several pairs of these electrodes to a small circular protractor. This made it possible, after the center of the protractor had been placed over the chosen point, to vary the position of the current axis in the manner desired by selecting the proper pair of connections instead of by removing and replacing the electrodes. We shall speak of the input as vertical when the current axis was parallel to the midsternal line, and as horizontal when this axis was perpendicular to this line.

Since alternating current was employed, the current axis had one direction during one-half of the cycle and exactly the opposite direction during the other half. The deflections recorded by the various leads used are, therefore, sine waves (considerably distorted in some instances). The measurements given represent the full amplitude of these waves minus the width of the light beam, which is about 2.0 millimeters. Plus and minus signs have been assigned to these measurements in such a way as to fulfill Einthoven's law whenever this law could be applied. In some instances each lead was taken simultaneously with Lead I, and when this was done deflections which were in phase with those of Lead I were considered positive and deflections which were 180° out of phase with those of Lead I were considered negative, or vice versa. For reasons which will appear later, the deflections of Leads RR, LL, and FF were made opposite in sign to those of unipolar Leads V_R, V_L, and V_F, respectively, except when the current axis was parallel to the sagittal plane, in which case they were considered all positive or all negative.

AN ILLUSTRATIVE EXPERIMENT

The experiment illustrated in Figs. 2,*A* and 2,*B* and summarized in Table I was performed on Sept. 24, 1946. A current of 0.5 milliampere was passed through the trunk by way of electrodes 1.1 cm. in diameter, which were equidistant from a point 4.0 cm. to the left of the midsternal line and at the level of the fourth intercostal space. The distance between them was 5.0 centimeters. The various leads were taken with the current axis horizontal and repeated after this axis had been rotated clockwise through 30, 60, 90, 120, and finally 150 degrees. The deflections in each of the records were measured and Einthoven's manifest potential difference, *E*, and the angle made by the electrical axis with the horizontal were computed in the customary way for each set of standard limb

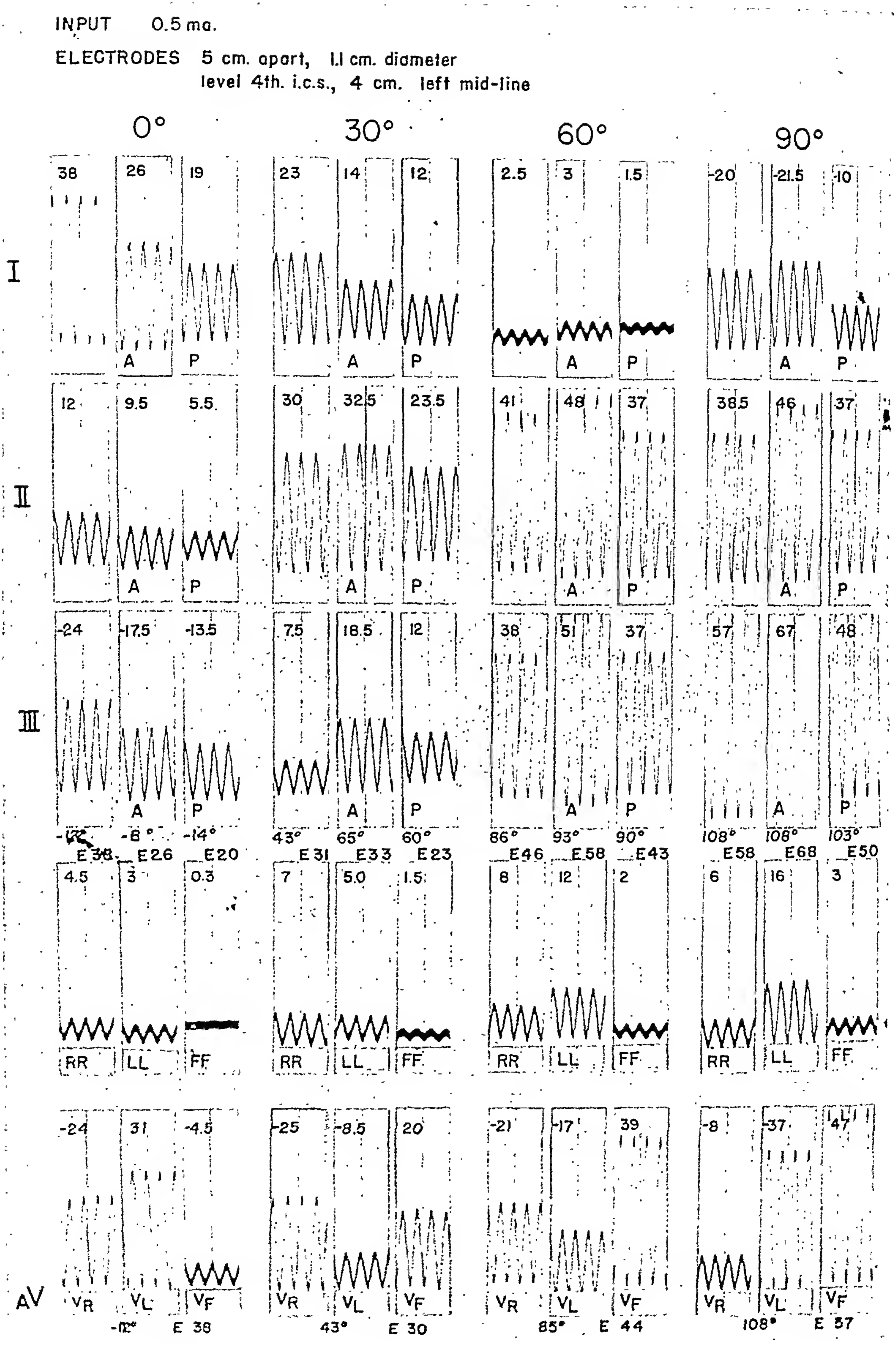


Fig. 2.—A. Experiment 3, b. Input electrodes to the left of the midline. Deflectons in the various leads
...e angle made by the current axis with the horizontal was 0, 30, 60, and 90 degrees, respectively.

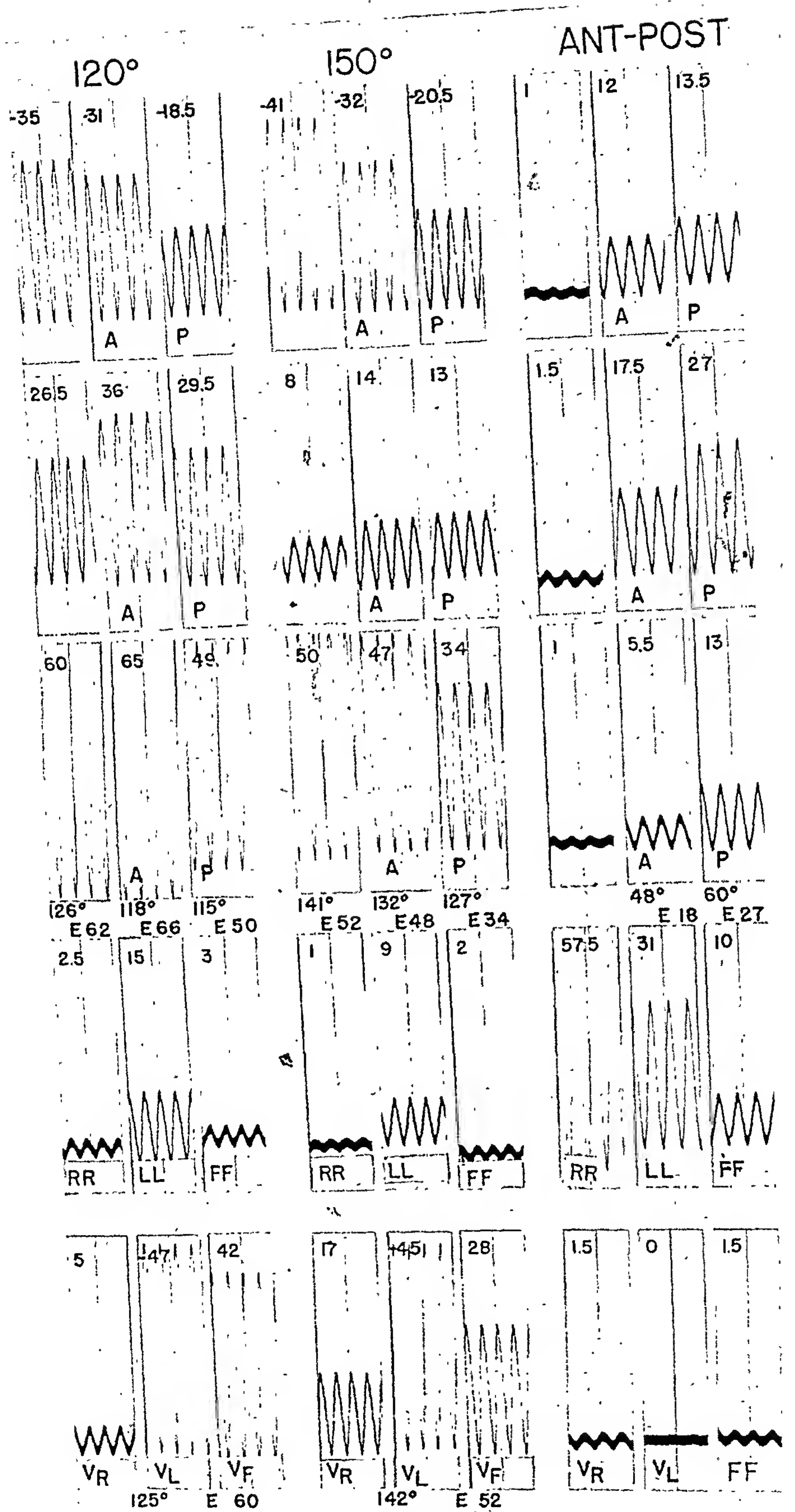


Fig. 2.—*B*, Experiment 3, *b*. Continuation of Fig. 2, *A*. Deflections in the various leads when the angle between the current axis and the horizontal was 120 and 150 degrees, and anteroposterior when one input electrode was on the back and the other on the front of the chest.

leads, unipolar limb leads, anterior leads, and posterior leads. The values for these quantities which appear in Figs. 2,*A* and 2,*B* were obtained graphically. Those which are given in Table I were computed. In the case of those measurements which did not fulfill Einthoven's law, the measurement for Lead III was revised, for the purpose of these computations, to the extent required to bring it into accord with those for Leads I and II.

The last set of leads shown in Fig. 2,*B* was taken at the end of the experiment for the purpose of studying the field produced by a sagittal current axis. One electrode was placed on the front of the chest, at the level of the fourth intercostal space and over the right margin of the sternum, and the other on the back, close to the seventh dorsal spine. The two input electrodes were then far apart and, since the current was not reduced, the electrical moment was much greater than when the other records were taken. It will be noted that the deflections in the standard limb leads are extremely small; in other experiments it was found that they could be abolished altogether by moving one of the input electrodes a short distance in one direction or another. It was never possible, however, to bring the deflections to zero in all of the standard limb leads and in all of the anterior or posterior leads at the same time. When the current axis has a sagittal direction the deflections in the sagittal leads, RR, LL, and FF, are naturally larger than when this axis is parallel to, or makes a small angle with, the frontal plane. In the few experiments of this kind performed, however, the deflections in Lead FF were always smaller, and usually much smaller, than those of Leads RR and LL.

Before discussing other aspects of this experiment we shall explain the figures enclosed in parentheses in Table I. In general, any number of forces acting at the same point can be added vectorially according to the parallelogram law, or can be regarded as equivalent to three forces each parallel to one axis of a system of mutually perpendicular axes equal in number to the dimensions of the space under consideration. It has always been held that the electromotive force of the heart at a given instant is a directed quantity of this kind, and this view is certainly correct if the electrical field of the heart is equivalent to that of a mathematical dipole, as Einthoven and his associates assumed. In the experiment under consideration, the distance between the positive and negative poles was not, as in the case of such a dipole, extremely small in comparison with the distance of the lead electrodes from them. It seemed desirable, therefore, to ascertain whether, for example, a current input of 0.3 milliamperes at 30 degrees was equivalent, under these circumstances, to a current input of 0.3 cos 60° milliamperes at 0 degrees plus a current input of 0.3 sin 60° milliamperes at 90 degrees. The cosine of 60 degrees is 0.5 and the sine 0.866. If we multiply the observed deflection in Lead I listed under 0 degrees in the table by the former, we obtain the figure 19.0. The deflection for the same lead listed under 90 degrees is −20.0, and this multiplied by 0.866 gives −17.32. The expected deflection in Lead I for a current axis of 60 degrees is then the algebraic sum of these two figures, or 1.68. The observed value is 2.5. For a current axis of 30 degrees the deflection in Lead I measured 23.0 millimeters. The calculated amplitude of this deflection is 22.9 millimeters. If the other figures given in the

TABLE I. MAGNITUDE OF DEFLECTIONS, MANIFEST POTENTIAL DIFFERENCE (E), AND THE ANGLE MADE BY THE ELECTRICAL AXIS WITH THE HORIZONTAL AS DETERMINED IN EXPERIMENT 3b.

CURRENT AXIS	0°		90°		30°		60°		120°		150°		ΔP
LEAD													
I	38.0		−20.0		23.0		2.5		−35.0		−41.0		1.0
					(22.9)		(1.7)		(−36.3)		(42.9)		
II	12.0	−12°	38.5	110°	30.0	42°	41.0	82°	26.5	125°	8.0	141°	1.5
		38.9		59.4	(29.6)	31.1	(39.3)	42.4	(27.3)	63.8	(8.8)	55.3	
III	−24.0		57.0		7.5		38.0		60.0		50.0		1.0
					(6.7)		(37.6)		(63.6)		(51.8)		
IA	26.0		−21.5		14.0		−3.0		−31.0		−32.0		12.0
					(11.8)		(−5.6)		(−31.6)		(−33.2)		
IIA	9.5	−9°	46.0	108°	32.5	68°	48.0	96°	36.0	118°	14.0	132°	17.5
		26.3		69.0	(31.2)	31.5	(44.5)	54.1	(35.1)	67.3	(14.8)	49.1	
IIIA	−17.5		67.0		18.5		51.0		65.0		47.0		5.5
					(19.6)		(50.2)		(66.7)		(48.0)		
IP	19.0		−10.0		12.0		1.5		−18.5		−20.5		13.5
					(11.5)		(0.8)		(−18.2)		(−21.5)		
IIP	5.5	−14°	37.0	102°	23.5	60°	37.0	89°	29.5	112°	13.0	127°	27.0
		19.2		49.5	(23.3)	23.4	(34.8)	39.2	(29.3)	48.2	(13.7)	35.4	
IIIP	−13.5		48.0		12.0		37.0		49.5		34.0		13.0
					(11.8)		(34.0)		(47.4)		(35.2)		
AV_R	−24.0		−8.0		−25.0		−21.0		5.0		17.0		1.5
AV_L	31.0		−37.0		8.5		−17.0		−47.0		−15.0		0
AV_F	−4.5		47.0		20.0		40.0		42.0		28.0		1.5
RR	4.5		6.0		7.0		8.0		−2.5		−1.0		57.5
					(6.9)		(7.5)		(−2.9)		(0.9)		
LL	−3.0		16.0		−5.0		12.0		15.0		9.0		31.0
					(−5.4)		(12.3)		(15.3)		(10.6)		
FF	0.3		−3.0		−1.5		−2.0		−3.0		−2.0		10.0
$(V_T)_P - (V_T)_A$	0.6		6.3		0.2		6.0		4.8		2.0		

The theoretical magnitudes of the deflections are shown in parentheses directly below the observed magnitudes.

For each set of standard limb leads, anterior leads, and posterior leads, the manifest potential difference E and the angle which gives the position of the electrical axis, found by the customary method, are given following the figure for the deflection in Lead II, Lead IIA, and Lead IIP.

table are examined it will be seen that, considering all the possibilities of error involved, the agreement between the observed and calculated deflections is surprisingly good. Hereafter, when the distance between the input electrodes was not greater than 5 cm., we shall confine the discussion chiefly to the tracings obtained when the current axis was horizontal and those obtained when it was vertical. It will be convenient to use the letter H to designate the former and the letter V to designate the latter. Such symbols as $(I)_H$, $(II)_H$, $(II)_V$, and $(III)_V$ will be used to represent the deflections in the various leads under these two different conditions.

The sagittal leads RR, LL, and FF measure the differences in potential between the apices of the triangle formed by the posterior leads and the corresponding apices of the triangle formed by the anterior leads. These relations are expressed by the following equations:

$$(6) \quad (V_R)_P - (V_R)_A = RR$$
$$(7) \quad (V_L)_P - (V_L)_A = LL$$
$$(8) \quad (V_F)_P - (V_F)_A = FF$$

Here the symbol $(V_R)_P$ represents the true potential of the electrode on the posterior aspect of the right shoulder and the other symbols have a like significance. If these equations are added and the sum is divided by three, we obtain the expression

$$(9) \quad 1/3\,[(V_R)_P + (V_L)_P + (V_F)_P)] - 1/3\,[(V_R)_A + (V_L)_A + (V_F)_A] = 1/3\,(RR + LL + FF)$$

or, what amounts to the same thing,

$$(10) \quad (V_T)_P - (V_T)_A = 1/3\,(RR + LL + FF)$$

where $(V_T)_P$ is the potential of a central terminal connected through equal resistances to the three posterior electrodes, and $(V_T)_A$, the potential of central terminal connected through equal resistances to the three anterior electrodes. When the sum in the second member of this equation is positive, the anterior terminal is negative with respect to the posterior.

In Table I the figure obtained by adding the deflections in Leads RR, LL, and FF algebraically and dividing the sum by 3 is given for each position of the current axis. Observe that the calculated difference in potential between the two central terminals was small when the current axis was horizontal or nearly so, and relatively large when this axis was vertical or nearly vertical. The anterior terminal is negative with respect to the posterior for all of the positions of the current axis listed.

There is a rough correspondence between the relative size of the deflections in the unipolar leads from the two arms and the relative size of the deflections in Leads RR and LL. In the three instances in which the deflections in Lead aV_L are very much larger than the deflections in Lead aV_R, the deflections in Lead LL are much larger than those in Lead RR (Table I, columns headed 90, 120, and 150). In one instance (Column 30) the deflections in Lead aV_R are much larger than those of Lead aV_L and the deflections of Lead RR are somewhat larger than those of Lead LL. In the other two cases this relation does not hold;

in one of them (Column 0) the deflections of Lead aV_L are considerably larger than those of Lead aV_R, but the deflections of Lead LL are smaller than those of Lead RR; in the other (Column 60) the opposite is true. The deflections in Lead FF are very small for every position of the current axis and it is difficult to demonstrate any relation of the kind in question between this lead and Lead aV_F.

Compared to the apices of the anterior triangle, the corresponding apices of the posterior triangle are more distant from the input electrodes but otherwise similarly situated with respect to them. One would, therefore, expect that when the potential of a given apex of the former became positive or negative the potential of the corresponding apex of the latter must show a fluctuation of the same sign but of smaller magnitude. The coccygeal and pubic electrodes are farther apart than the two electrodes of the other two pairs, but they are also much farther from the precordium. Does this account for the smallness of the deflections in Lead FF? Are the potential variations of the leg electrode regularly smaller than those of the arm electrodes even when the current axis is vertical? These questions cannot be answered now, but we are confident that they can be answered in the near future.

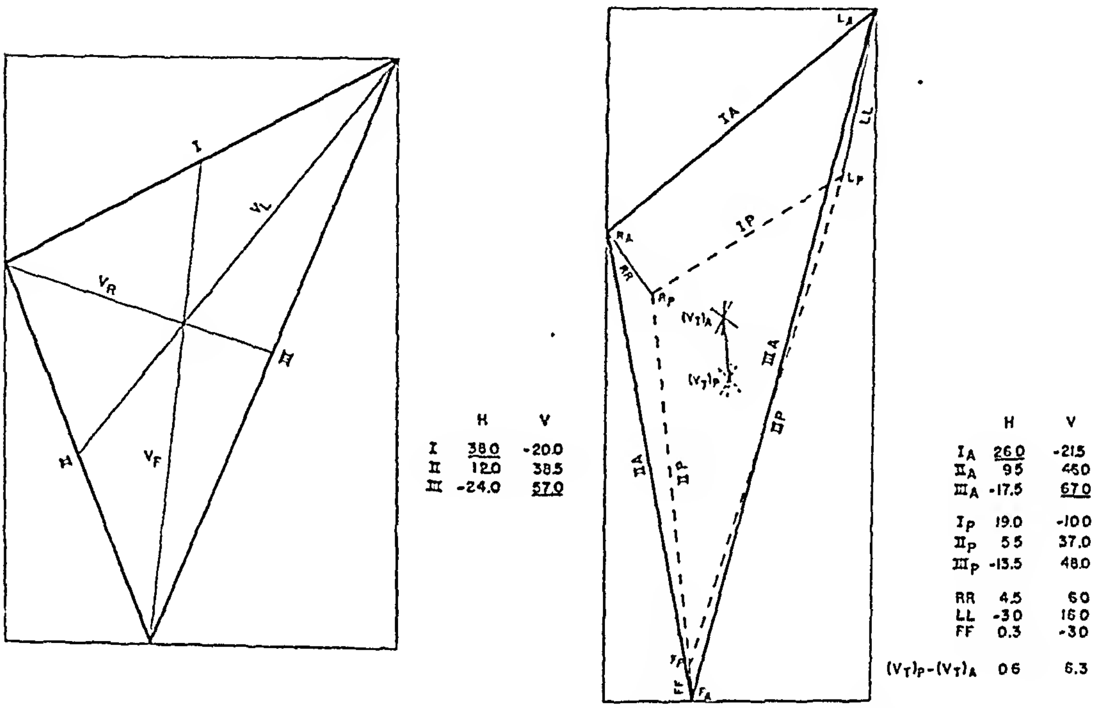
CONSTRUCTION AND USE OF THE BURGER TRIANGLE

Referring once more to the data shown in Table I, we may point out that the magnitude of Einthoven's manifest electromotive force (E) shows striking variations with the position of the current axis. It is much larger for a vertical than for a horizontal axis and is greatest when the current flow is parallel to Lead III (120 degrees). There are also pronounced discrepancies between the position of the axis defined by the input electrodes and the position of the electrical axis calculated in the customary manner. When the former axis made an angle of 60 degrees with the horizontal, the latter was separated from it by an angle of 22 degrees when the calculations were based on the standard limb leads; 36 degrees when they were based on the anterior leads; and 29 degrees when they were based on the posterior leads. For this position of the current axis the deflections in Leads I, IA, and IP were very small so that the calculated axis was nearly perpendicular to these leads.

For both horizontal and vertical current flow, the deflections in Lead III were larger than those in Lead II and the deflections in Lead aV_L were larger than those in Lead aV_R. It is apparent, therefore, that the differences between the true situation existing in this experiment and that which Einthoven and his associates postulated should be attributed to the eccentric position of the input electrodes. These were placed to the left of the midsternal line, and the left shoulder, being closer to the source of the field than the right, displayed larger potential variations than its fellow.

The methods devised by Burger and Van Milaan[4] make it possible to present practically all of the significant data pertaining to Experiment 3,*b* in a single diagram (Fig. 3). They regard the deflection in a given lead as the scalar product of two vectors, one of which represents that lead and the other the electromotive force responsible for the field. In the Gibb's notation the scalar, or dot, product

of two vectors, **A** and **B**, is written **A·B** in clarendon type. The value of this expression is obtained by multiplying the product of the lengths of the two vectors by the cosine of the angle between the positive direction of the one and the positive direction of the other. This amounts to the same thing as multiplying the length of one vector by the projection of the other upon it. When one vector is of unit length the scalar product is equal to the length of the other multiplied by the cosine of the angle between the directions which the two vectors define.



	H	V
I	38.0	-20.0
II	12.0	38.5
III	-24.0	57.0

	H	V
I_A	26.0	-21.5
II_A	9.5	46.0
III_A	-17.5	67.0
I_P	19.0	-10.0
II_P	5.5	37.0
III_P	-13.5	48.0
RR	4.5	6.0
LL	-3.0	16.0
FF	0.3	-3.0
$(V_T)_P-(V_T)_A$	0.6	6.3

Fig. 3.—Experiment 3, *b*. Diagrams, constructed by the method of Burger and Van Milaan,[4] which depict in graphic form the material shown in Figs. 2, *A* and 2, *B* and in Table I.

In the present discussion we need not be concerned with the absolute, but only with the relative lengths of the vectors with which we shall have to deal. We may, therefore, consider that one which represents the electromotive force as of unit length. When this is done the deflection in any lead is the product of the length of that lead and the cosine of the angle which its positive direction makes with that of the current axis. The problem of finding the vectors which depict the leads used in our experiment then becomes a relatively simple one, for we know for each of these leads the size of the deflections both when the current axis was horizontal and when it was vertical. In the one case the unit vector points from right to left (0 degrees) and in the other it points straight down (90 degrees). The direction of Lead I, for example, with respect to the first of these unit vectors, is defined by the angle of which the tangent is equal to $(I)_V$ divided by $(I)_H$, or $-20/38$ (Table I). Performing the indicated operation, we obtain the figure -0.5263, and on consulting a table of the natural trigonometric functions find that the angle sought is approximately -28 degrees. The length of Lead I, which gives the size of the deflection in this lead, when the

current axis is parallel to it and may, therefore, be represented by the symbol $(E)_I$, can be found by adding the squares of $(I)_V$ and $(I)_H$ and extracting the square root of the sum thus obtained. In the present instance this calculation gives the figure 42.94. Table II gives the length and direction with respect to the horizontal of each of the twelve leads used in the experiment under consideration.

TABLE II. LENGTH AND DIRECTION, WITH RESPECT TO THE HORIZONTAL, OF THE TWELVE LEADS USED

LEAD	LENGTH	ANGLE (DEGREES)
I	42.9	−28
II	40.3	73
III	64.0	114
IA	33.7	−40
IIA	47.0	78
IIIA	70.0	103
IP	21.5	−28
IIP	37.0	81
IIIP	50.0	109
RR	7.5	53
LL	16.3	101
FF	3.0	−84

The rather tedious computations involved in this method can be avoided by the use of a straightedge, square, and ruler. To construct a given lead, proceed as follows: On a horizontal line lay off a segment of a length equal to the amplitude of the deflection for a horizontal input. If this deflection is positive, draw a vertical line through the right, and if it is negative, through the left end of this segment. On this vertical line measure from the horizontal line a length equal to the amplitude of the deflection for a vertical input. This second segment should extend downward when this deflection is positive, and upward when it is negative. Draw the hypotenuse of the right triangle of which these two segments are the perpendicular sides. This line represents the lead vector and its positive direction is from the beginning of its horizontal to the end of its vertical component.

In constructing a diagram such as that shown in Fig. 3, it is, of course, necessary to find only those lead vectors that are independent. When the lead vectors already drawn are sufficient to locate all the electrodes, the others can be found by drawing lines between the points representing the electrodes which they connect.

The augmented unipolar limb leads are represented by the medians of the triangle corresponding to the standard limb leads. The unaugmented unipolar limb leads are those segments of these medians lying between their intersection and the apices of the triangle. The medians of the anterior and the posterior triangle have a similar significance. The vector drawn from the intersection of the medians of the former to the intersection of the medians of the latter depicts a lead from the central terminal of the first to that of the second.

To avoid a possible misunderstanding it should be emphasized that the nine lead diagram of Fig. 3 is not an attempt to reproduce a three dimensional figure upon a flat surface. The sagittal leads RR, LL, and FF appear in this diagram only because they showed deflections when the current axis was parallel to the frontal plane. In other words, these leads had components in the frontal plane, and it is these that appear in the diagram. The sagittal components of these leads, by virtue of which they displayed deflections when the current axis was parallel to the sagittal plane, are not shown.

When the deflections in two of the three leads of an oblique triangle are known, the direction and length of the vector which represents the electromotive force acting can be found. The method of doing this is somewhat different from that employed in the case of an equilateral triangle and requires some words of explanation.

The scalar product of two vectors, **A** and **B**, is equal to the sum of the scalar products obtained by multiplying each of the mutually perpendicular components of the one by the corresponding component of the other; that is,

$\mathbf{A}\cdot\mathbf{B} = a_1b_1 + a_2b_2$, where a_1 is the length of the horizontal component of **A**, b_1 is the length of the horizontal component of **B**, and a_2 and b_2 are the lengths of the vertical components of **A** and **B**, respectively.

Let us assume that Leads I and II are those for which the deflections are known. Let D_I and D_{II} stand for these known deflections, and X and Y for the horizontal and vertical components of the unknown electromotive force. We may then form the following equations:

(11) $D_I = (I)_H X + (I)_V Y$

(12) $D_{II} = (II)_H X + (II)_V Y$

The second member of each of these equations is the sum of the product of the horizontal components of the lead vector and the electromotive force and the product of their vertical components. These equations can easily be solved for the unknowns, X and Y. If the first is divided by the length of Lead I and the second by the length E_{II} of Lead II, we obtain:

(13) $$\frac{D_I}{E_I} = \frac{(I)_H X}{E_I} + \frac{(I)_V Y}{E_I}$$

(14) $$\frac{D_{II}}{E_{II}} = \frac{(II)_H X}{E_{II}} - \frac{(II)_V Y}{E_{II}}$$

These last equations show that the deflection in a given lead divided by its length is equal to the sum of the projections of the horizontal and vertical components of the electromotive force, and, therefore, to the projection of this force as a whole upon that lead. In obtaining the magnitude and direction of the electromotive force graphically, the procedure in the case of the Burger triangle differs from that employed in the case of the Einthoven triangle in only one respect. The former does not have sides that are equal in length and each of the known deflections must be divided by the length of the lead to which it belongs before operations are begun.

EFFECT OF THE POSITION OF THE INPUT ELECTRODES WITH REFERENCE TO THE MIDLINE UPON THE FORM OF THE BURGER TRIANGLE

Five experiments were performed upon Subject 4 and these are designated by the symbols 4,*b*, 4,*c*, 4,*d*, 4,*e*, and 4,*f*. In all these experiments the input electrodes (1.1 cm. in diameter) were at the same vertical level (fourth intercostal space at the sternal margin) and the current passed through them was 0.5 milliamperes. In three instances they were 5.0 cm. apart (4,*b*, 4,*d*, and 4,*f*); in the first of these, the point midway between them was 5.0 cm. to the right of the mid-

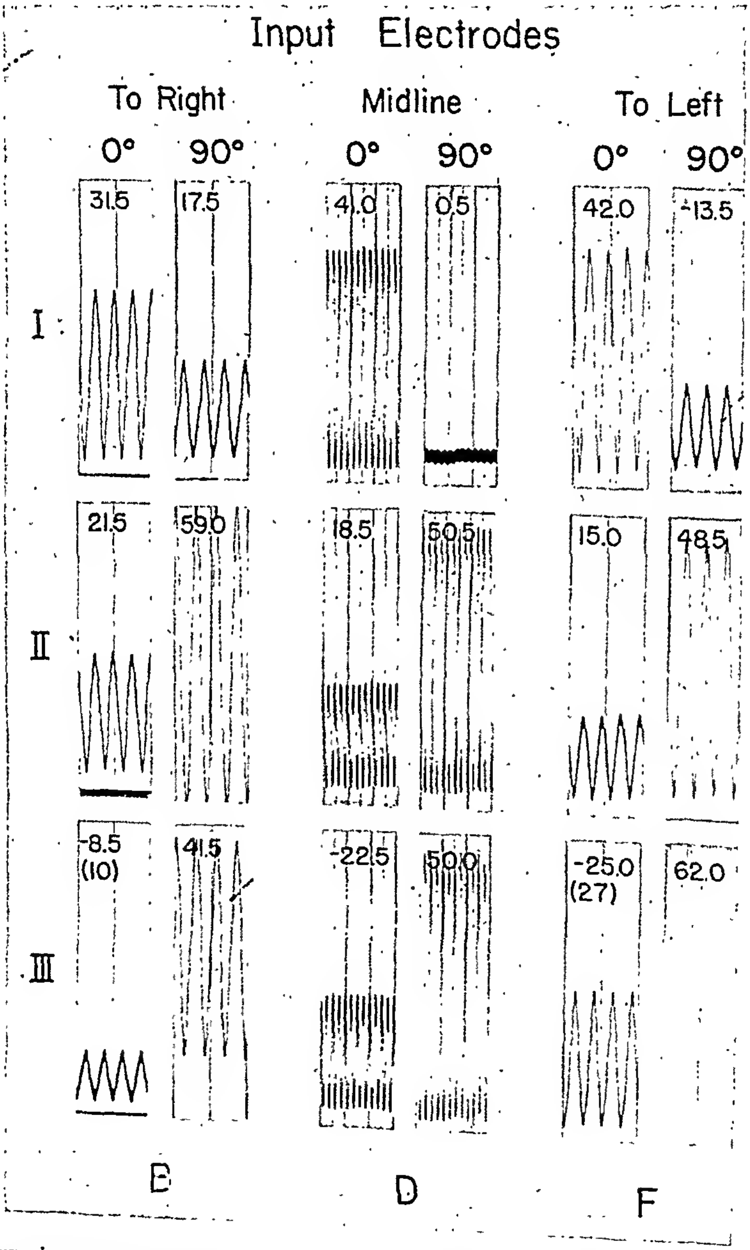


Fig. 4.—Experiments 4, *b*, 4, *d*, and 4, *f*. Input electrodes to the right of the midline in 4, *b*, in the midline in 4, *d*, and to the left of the midline in 4, *f*. The deflections in the standard limb leads when the current axis was horizontal (0°) and when it was vertical (90°).

sternal line, in the second it was on this line, and in the third it was 5.0 cm. to the left of it. The tracings obtained in these three experiments when the current axis was horizontal and when it was vertical are reproduced in Fig. 4, and the corresponding triangles are shown in Fig. 5. Experiments 4,*c* and 4,*e* were identical with Experiments 4,*b* and 4,*d*, respectively, except that the distance between

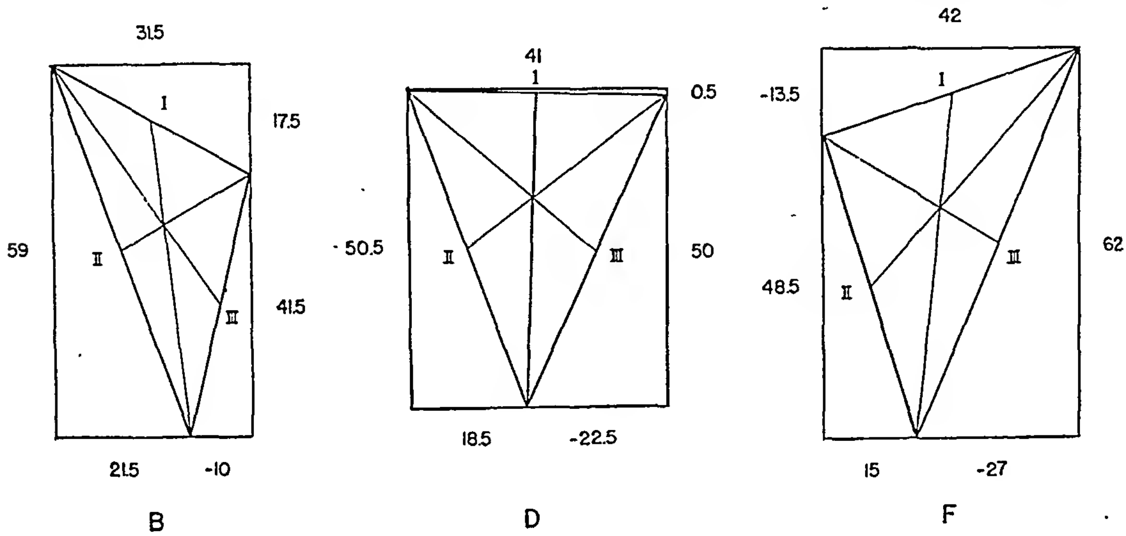


Fig. 5.—The Burger triangles corresponding to the deflections shown in Fig. 4.

the input electrodes was 2.0 cm. instead of 5.0 centimeters. The effects of this reduction in the electrical moment are summarized in Table III, which gives for all of the five experiments the amplitudes of the deflections in the limb leads for two positions of the current axis, the length (E_I, E_{II}, etc.) of each lead vector, and the angle between it and the horizontal.

TABLE III. EFFECT OF REDUCTION OF DISTANCE BETWEEN INPUT ELECTRODES (ELECTRICAL MOMENT)

EXPERIMENT	INPUT ELECTRODES		DEFLECTIONS					
	POSITION	DISTANCE APART	LEAD I		LEAD II		LEAD III	
			0 H	90 V	0 H	90 V	0 H	90 V
4b	5 cm. right	5 cm.	31.5	17.5	21.5	59.0	−8.5	42.0
4c	5 cm. right	2 cm.	15.5	8.0	10.5	25.0	−4.5	15.5
4d	Midline	5 cm.	41.0	0.5	18.5	50.5	−21.5	50.0
4e	Midline	2 cm.	22.5	0.5	10.0	21.0	−12.5	20.5
4f	5 cm. left	5 cm.	42.0	−13.5	15.0	48.5	−25.0	62.0
			E_I	ANGLE (DEGREES)	E_{II}	ANGLE (DEGREES)	E_{III}	ANGLE (DEGREES)
4b	5 cm. right	5 cm.	36.0	29	62.8	70	43.2	103
4c	5 cm. right	2 cm.	17.6	27	27.1	67	16.1	106
4d	Midline	5 cm.	41.0	0	53.3	70	54.4	114
4e	Midline	2 cm.	22.5	0	23.2	65	23.9	121
4f	5 cm. left	5 cm.	44.1	−18	50.8	73	67.3	113

It is of interest that when we reduced the distance between the input electrodes from 5.0 to 2.0 cm., without altering the size of the current flowing, the amplitude of the deflections fell somewhat more than 50 per cent, on the average, but the shape of the Burger triangle did not materially change.

When the point midway between the centers of the electrodes was on the midsternal line, the triangle was isosceles, or very nearly so, with the side corresponding to Lead I shorter than those corresponding to Leads II and III. When this point was to the right of the midline, Lead II was longer than Lead III and the angle which defines the direction of Lead I was positive; when it was to the left of the midline, Lead III was larger than Lead II and the angle between Lead I and the horizontal was negative. There can be no doubt that in the first of these three cases the potential variations of the two arms were of approximately the same magnitude. In the second the potential variations of the right arm were greater than those of the left for both positions of the current axis; in the third the reverse was true.

ON SEPARATING THE HORIZONTAL AND VERTICAL COMPONENTS OF THE FIELD AND BRINGING THE POTENTIAL OF THE CENTRAL TERMINAL TO ZERO

In Experiment 4,*d* the Burger triangle was very close to isosceles (Fig. 5). Let us make it exactly so by equalizing the absolute magnitudes of the deflections in Leads II and III; this process gives for the amplitudes of the deflections in the various leads the following figures:

$(I)_H$	$(II)_H$	$(III)_H$	$(V_R)_H$	$(V_L)_H$	$(V_F)_H$
41.0	20.5	−20.5	−20.5	20.5	0
$(I)_V$	$(II)_V$	$(III)_V$	$(V_R)_V$	$(V_L)_V$	$(V_F)_V$
0	50.3	50.3	−16.7	−16.7	33.4

In this case, it is clearly possible to separate the horizontal and the vertical components of the electromotive force, for the purpose, for example, of obtaining an accurate vectorcardiogram. Lead I yields a deflection of 41 mm. when the current axis is horizontal and no deflection when this axis is vertical. Lead V_F gives a deflection of 33.4 mm. when the current axis is vertical and no deflection when it is horizontal. By recording Lead I with the "horizontal channel" of the vectorcardiograph operating at its "normal" sensitivity, and Lead V_F simultaneously with the "vertical channel" of the vectorcardiograph operating at a sensitivity 41/33.4 times as great, we should obtain an accurate record of the changes in the position of the electrical axis.

When the current axis was horizontal the deflection in Lead V_F was zero; that is, the central terminal and the left leg were at the same potential. The spatial relations between the input electrodes and the junctions of the limbs with the trunk were such that there can be no doubt that this potential was zero in the sense that it was midway between that of the region where the current entered and that of the region where the current left the body. On the other hand, the shape of the Burger triangle indicates that when the current axis was vertical the potential of the central terminal was not zero in this sense. It may seem

probable that the shape and dimensions of the triangle, which are given, supply the data necessary for the computation of the potential of this terminal, but this is not the case, unless it be assumed that the point midway between the input electrodes was "electrically" equidistant from the limb electrodes. Actually, this point was much farther, in the geometric sense, from the junction of the left leg with the trunk than from the junctions of the arms with the trunk. The assumption mentioned amounts to the supposition that the field in this experiment was equivalent to that of a centric dipole in a homogeneous conducting sphere. In the case of a model of this kind, and leads from electrodes that are equidistant from the center of the homogeneous spherical volume conductor, the Burger triangle and the geometric triangle defined by the three lead electrodes are similar in the technical Euclidean sense; each side of the one is parallel to the corresponding side of the other. Under the circumstances specified, the same statement holds for other figures, including the Burger tetrahedron and the corresponding geometric tetrahedron defined by four lead electrodes not all in the same plane. Under all other circumstances, the Burger triangle or tetrahedron, as the case may be, differs in shape from the geometric triangle or tetrahedron of which the lead electrodes are the apices.

If we make the assumption in question, the potential of the central terminal when the current axis was vertical can be found in the following way: The tangent of half the angle at that apex of the isosceles triangle corresponding to the leg electrode is given by the ratio $\frac{{}^1/_2(I)_H}{(II)_V}$, or $\frac{20.5}{50.3}$, which is equal to 0.4075. This is the tangent of 22 degrees. Knowing this angle, we can find the other angles of the triangle. The angle made with the horizontal by the radius vector from the center of the circle defined by the apices of the triangle to that apex which corresponds to the electrode on the left arm is 90 degrees minus 44 degrees, or 46 degrees. The true potential of this electrode when the current axis was vertical was, therefore, R sin −46 degrees where R is the radius of the circle mentioned and therefore the length of the leads from the center of this circle to the apices of the triangle. Since the true potential of the leg electrode was consequently R cos 0 degrees when the current axis was vertical, we have the equation

$$R \cos 0^\circ - R \sin -46^\circ = (II)_V$$

or

$$R(1 + 0.695) = 50.3, \text{ and } R = 29.7$$

The true potential of the left leg was then 29.7 tenths of a millivolt and the true potential of the central terminal 29.7 minus 33.4 or −3.7 tenths of a millivolt. We have carried out this computation for the sake of introducing the problem of reducing the potential variations of the central terminal to zero. We do not believe that the assumption on which it is founded is valid.

In a preceding section of this paper, it was pointed out that the vectors drawn from the intersection of the medians of the Burger triangle to its apices represent the three unaugmented unipolar limb leads. Since these leads measure the potential of the limb electrodes with respect to that of the central terminal, we may consider each apex of this triangle at the same potential as the correspond-

ing extremity. We may likewise regard the intersection of the medians as at the same potential as a central terminal connected to the limb electrodes through equal resistances. With the midpoint of each side of the triangle we may associate a potential half-way between the potentials of the apices it connects. We may suppose that along each side and each median of the triangle the potential falls uniformly from the end of that side or median where it is higher to the end where it is lower. Every point inside the triangle is then at a potential which may be regarded as a weighted mean of the potentials of its apices. When the dipole responsible for the field and the lead electrodes lie in the same plane and the dipole is inside the geometric triangle which these electrodes define, one of the points of the corresponding Burger triangle is at zero potential for every position of the dipole axis. When the dipole is outside the electrode triangle it is clear that all of its apices, and, consequently, all points inside the Burger triangle, must be positive for some positions of the electrical axis and negative for others.

When the resistances in the arms of the central terminal are equal, its potential is the mean of the potentials of the apices of the triangle. By making these resistances unequal and giving them the proper relative magnitude, it is, however, possible to make the potential of the central terminal equal to that of any point on the perimeter of the triangle or inside it. We may regard CR, CL, and CF leads as leads from a central terminal connected to two apices of the triangle by infinite resistances. In this case, the potential of the terminal is the same as that of the third apex. Augmented unipolar limb leads are leads from a central terminal with equal resistances in two of its branches and an infinite resistance in the third. In this case, the reference potential is that of the midpoint of one of the sides of the triangle. By varying one of the three resistances without altering the other two, we can make this potential equal to that of any point lying on the median which runs from the apex corresponding to the altered resistance to the midpoint of the opposite side. The same result is obtained by leaving this resistance unchanged and altering the other two in equal measure. By making one resistance infinite and varying one of the others, we can give the central terminal a potential equal to that of any point on the side of the triangle opposite to the apex that has been disconnected. By making unequal changes in two of the three resistances, we can shift the potential of the terminal to that of any point lying inside any of the circumscribed areas into which the medians divide the triangle.

The change in the potential of the central terminal effected by a specified alteration of the relative magnitudes of the resistances in its three branches may be computed in the following way: Consider the equations:

$$(15)\quad 1/r_a\,(V_R - V_T^1) = i_a$$
$$(16)\quad 1/r_b\,(V_L - V_T^1) = i_b$$
$$(17)\quad 1/r_c\,(V_F - V_T^1) = i_c$$

in which r_a, r_b, and r_c are the resistances between the central terminal and the junctions with the trunk of the right arm, left arm, and left leg, respectively; V_T^1 is the potential of this terminal when these resistances are unequal; V_R, V_L, and V_F are the open circuit potentials of the three extremities; and i_a, i_b, and i_c

are the currents flowing toward the central terminal through the corresponding resistances. By Kirchhoff's current law, the sum of these three currents is zero, and if we add Equations 15, 16, and 17 and multiply by $r_a r_b r_c$, we obtain the expressions:

$$(18)\quad r_b r_c (V_R - V_T^1) + r_a r_c (V_L - V_T^1) + r_a r_b (V_F - V_T^1) = 0$$

and
$$(19)\quad V_T^1 = \frac{r_b r_c V_R + r_a r_c V_L + r_a r_b V_F}{r_b r_c + r_a r_c + r_a r_b}$$

When the three resistances are equal the potential of the central terminal, (V_T) is given by:

$$(20)\quad V_T = \frac{V_R + V_L + V_F}{3}$$

and
$$(21)\quad V_T^1 - V_T = \frac{r_b r_c (V_R - V_T) + r_a r_c (V_L - V_T) + r_a r_b (V_F - V_T)}{r_b r_c + r_a r_c + r_a r_b}$$

Since

$$(22)\quad r_a r_b (V_F - V_T) = -r_a r_b (V_R - V_T) - r_a r_b (V_L - V_T)$$

it follows that

$$(23)\quad V_T^1 - V_T = \frac{r_b (r_c - r_a)(V_R - V_T) + r_a (r_c - r_b)(V_L - V_T)}{r_b r_c + r_a r_c + r_a r_b}$$

$$(24)\quad V_T^1 - V_T = \frac{\left(\frac{r_c}{r_a} - 1\right)(V_R - V_T) + \left(\frac{r_c}{r_b} - 1\right)(V_L - V_T)}{\frac{r_c}{r_a} + \frac{r_c}{r_b} + 1}$$

It is convenient to have also expressions for the currents i_a, i_b, and i_c in terms of the open circuit voltages (I), (II), and (III) in the three limb leads and the resistances r_a, r_b, and r_c. For certain purposes the internal resistances between the junctions of the extremities with the trunk must be considered. We shall here regard these as equal and small in comparison with the external resistances (r_a, r_b, and r_c) and represent them by the symbol r_1. The expressions referred to are given in a previous paper from this laboratory.[5] The currents mentioned appear in them as fractions with the denominator

$$(25)\quad r_1^2 + 2r_1 (r_a + r_b + r_c) + 3 (r_a r_b + r_a r_c + r_b r_c)$$

Representing this denominator by k we have:

$$(26)\quad k i_a = -(r_1 + 3r_c)(I) - (r_1 + 3r_b)(III)$$
$$(27)\quad k i_b = (r_1 + 3r_c)(I) - (r_1 + 3r_a)(II)$$
$$(28)\quad k i_c = (r_1 + 3r_b)(II) + (r_1 + 3r_a)(III)$$

Equation 19 is true for all positions of the current axis and all values of V'_T, including the value zero. Consequently,

$$(29) \quad r_b r_c\,(V_R)_H + r_a r_c\,(V_L)_H + r_a r_b\,(V_F)_H = 0$$

$$(30) \quad r_b r_c\,(V_R)_V + r_a r_c\,(V_L)_V + r_a r_b\,(V_F)_V = 0$$

These equations may be solved for the ratios r_a/r_c, r_b/r_c, and r_b/r_a, the last of which is the second divided by the first.

$$(31) \quad \frac{r_a}{r_c} = \frac{(V_R)_V(V_L)_H - (V_R)_H(V_L)_V}{(V_F)_H(V_L)_V - (V_F)_V(V_L)_H}$$

$$(32) \quad \frac{r_b}{r_c} = \frac{(V_L)_V(V_R)_H - (V_L)_H(V_R)_V}{(V_F)_H(V_R)_V - (V_F)_V(V_R)_H}$$

$$(33) \quad \frac{r_b}{r_a} = \frac{(V_F)_V(V_L)_H - (V_F)_H(V_L)_V}{(V_F)_H(V_R)_V - (V_F)_V(V_R)_H}$$

These are the relative magnitudes of the resistances required to bring the potential of the central terminal to zero when the true potentials of the limb electrodes are known for two positions of the current axis, provided that the dipole is inside the triangle.

When this triangle is isosceles $(V_F)_H$ is zero and Equation 33 gives

$$(34) \quad \frac{r_b}{r_a} = \frac{(V_L)_H}{-(V_R)_H} = \frac{-(III)_H}{(II)_H} = 1$$

and, since $(V_R)_V$ and $(V_L)_V$ are equal and $-(V_R)_H$ and $(V_L)_H$ are equal, Equations 31 and 32 give

$$(35) \quad \frac{r_a}{r_c} = \frac{2(V_R)_V}{(V_F)_V}$$

and

$$(36) \quad \frac{r_b}{r_c} = \frac{2(V_L)_V}{(V_F)_V}$$

These last equations are true not only when the triangle is isosceles, but also whenever $(V_F)_H$ is zero and $\frac{(V_R)_V}{(V_L)_V}$ is equal to $\frac{-(V_R)_H}{(V_L)_H}$; that is, whenever the lead vector V_F is parallel to the vertical axis and the angles made with this axis by the lead vectors V_R and V_L are equal.

We may now turn to a consideration of the triangles (Fig. 5) corresponding to Experiments 4,*b*, 4,*d*, and 4,*f*. For the last, we have for the deflections in the standard and unaugmented limb leads the following figures:

$(I)_H$	$(II)_H$	$(III)_H$	$(V_R)_H$	$(V_L)_H$	$(V_F)_H$
42.0	15.0	−27.0	−19.0	23.0	−4.0
$(I)_V$	$(II)_V$	$(III)_V$	$(V_R)_V$	$(V_L)_H$	$(V_F)_V$
−13.5	48.5	62.0	−11.7	−25.2	36.8

In this experiment, there were deflections in all of the leads used, both when the current axis was horizontal and when it was vertical. In cases of this kind, it is possible to alter the ratio r_b/r_a in such a way as to make the potential of the central terminal and that of the leg electrode equal when the current axis is horizontal. When these two potentials are equal the current i_c is zero.

According to Equation 28 we have, when ic is zero,

$$(37) \quad \frac{r_1 + 3r_b}{r_1 + 3r_a} = \frac{-(III)_H}{(II)_H}$$

or, when r_1 is neglected as negligibly small in comparison with $3r_a$ and $3r_b$,

$$(38) \quad \frac{r_b}{r_a} = \frac{-(III)_H}{(II)_H}$$

In the present instance, this equation gives for the magnitude of the ratio sought the figure 27/15, or 1.8. The result of the indicated alteration of the relative magnitude of the resistances involved would be to make the potential of the central terminal 4 units less positive and to reduce $(V_F)_H$ to zero. The horizontal component of the dipole would then produce no deflection in Lead V_F, and the deflection in this lead would be proportional to the vertical component. This procedure can be carried out whenever the deflection in Lead I, when the current axis is horizontal, is larger than the deflection in either of the other two limb leads. Under certain circumstances, it is possible to obtain a second lead which will yield a deflection proportional to the horizontal component of the dipole and no deflection for the vertical component by altering the ratios r_a/r_c and r_b/r_c in the manner required to make the currents i_a and i_b equal when the current axis is vertical. When the ratio i_b/i_a equals 1 we have from Equations 26 and 27 when the resistance r_1 is neglected

$$(39) \quad r_c\,(I)_V - r_a\,(III)_V = -r_c\,(I)_V - r_b\,(II)_V$$

$$(40) \quad \frac{r_a}{r_c} = \frac{-2(I)_V}{\frac{r_b}{r_a}\,(II)_V - (III)_V}$$

By substituting in this equation the values −13.5, 48.5, and 62 given for the deflections in Leads I, II, and III, respectively, when the current axis was vertical and the value 1.8 found for the ratio r_b/r_a, we obtain for r_a/r_c the value 1.067, and for the ratio r_b/r_c the value 1.92. A central terminal connected to the limb electrodes by resistances having these relative magnitudes would be 4 units less positive when the current axis was horizontal and 5.2 units less negative when this axis was vertical than a central terminal connected to these electrodes through equal resistances. Whenever i_a and i_b are equal, when the current axis is vertical, a lead from any point on the right-arm resistor to a point on the left-arm resistor, which is separated from the central terminal by the same resistance, will yield a deflection proportional to the horizontal component of the electromotive force; its vertical component will give rise to no potential difference between such points. In the present instance, the potentials with respect to the central terminal of the three points on its arms separated from it by a resistance equal to r_c have been computed for the two positions of the current axis. For a horizontal current axis, the figures are −15.0, 15.0, and 0, and for a vertical current axis they are −16.9, −16.9, and 33.8 for the points on the right arm, left arm, and leg resistor, respectively.

For the other experiments that have been referred to in this paper, the values of the ratios of the resistances in the arms of the central terminal required to make i_c zero when the current axis was horizontal, and i_a equal to i_b when this axis was vertical are as follows: for Experiment 4,*b*, r_a/r_b equals 2.2, r_a/r_c equals 2.5, and r_b/r_c equals 1.2; for Experiment 4,*c* the corresponding figures are 2.1, 3.1, and 1.5, respectively. For Experiment 3,*b* the values are r_b/r_a equals 2.2, r_b/r_c equals 3.5, and r_a/r_c equals 1.6. In all of these experiments, it would, therefore, have been possible to separate the horizontal and vertical components of the electromotive force for any position of the electrical axis by the methods proposed.

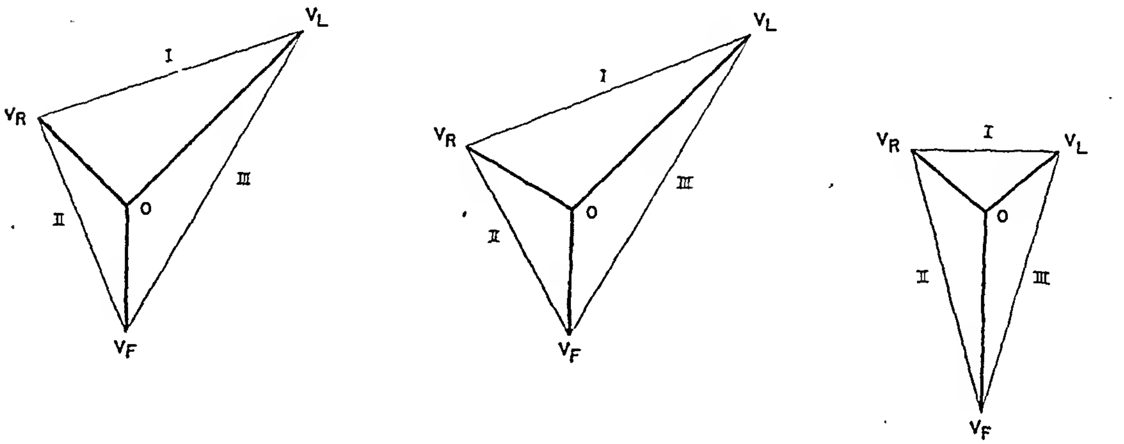
In order to make clear the limitations of these methods and the kind of cases in which they are applicable, we may consider three hypothetical triangles (Fig. 6). The values assumed for the true potentials of the three electrodes are for each of these triangles, as follows:

Triangle	$(V_R)_H$	$(V_L)_H$	$(V_F)_H$	$(V_R)_V$	$(V_L)_V$	$(V_F)_V$
(A)	−2.12k	4.24k	0	−2.12k	−4.24k	3k
(B)	−2.60k	4.24k	0	−1.5k	−4.24k	3k
(C)	−1.865k	1.865k	0	−1.506k	−1.506k	4.888k

The letter *k* is an arbitrary constant.

In the first case (A) the field is that of a centric dipole in a homogeneous medium. The angles between the radius vectors to the R and L apices of the triangle and the negative one-half of the vertical axis are both 45 degrees. The electrode at the first of these apices is on the surface of the medium, as is also the electrode at the F apex. The other electrode is enough closer to the centric dipole to make its potential variations twice as large as they would be if it too

were on this surface. The radius vector to the F electrode makes an angle of 0 degrees with the positive direction of the vertical axis. The methods described give for the ratios of the resistances in the arms of the central terminal the values r_b/r_a equals 2, r_a/r_c equals 1.414, r_b/r_c equals 2.828. These are the values required to reduce the potential of the central terminal to zero.



	A H	A V		B H	B V		C H	C V
VR	-2.12	-2.12	VR	-2.60	-1.50	VR	-1.87	-1.51
VL	4.24	-4.24	VL	4.24	-4.24	VL	1.87	-1.51
VF	0	3.00	VF	0	3.00	VF	0	4.88

A B C

Fig. 6.—Three hypothetical Burger triangles. (See text.)

In the second case (B), the field is again that of a centric dipole in a homogeneous spherical medium and the L electrode is in the same position as in Case (A); it is not at the surface of this medium as are the other two. The radius vector to the R apex makes an angle of 60 and that to the L apex an angle of 45 degrees with the negative direction of the vertical axis. The radius vector to the F apex again makes an angle of zero degrees with the positive direction of this axis. In this instance, the value of r_b/r_a required, when the current axis is horizontal, to make the potential of the central terminal and the current i_c zero is 1.633, and this is equal to $\frac{-(III)_H}{(II)_H}$, or $\frac{4.24}{2.60}$. On the other hand, the values of r_a/r_c and r_b/r_c required to make i_a and i_b equal, when the current axis is vertical, are 51.8 and 84.6, respectively. It is clearly not feasible to equalize these currents in cases of this kind. The values of r_a/r_c and r_b/r_c required to make the potential of the central terminal zero for a vertical current axis are 1.366 and 2.231, respectively. These are the values which make the ratio i_b/i_a equal to the ratio of minus tangent Θ_2 to tangent Θ_1, where Θ_2 is the angle between the positive direction of the horizontal axis and the radius vector to the L apex, and Θ_1 the corresponding angle between this axis and the radius vector to the R apex of the triangle. It is, nevertheless, possible to find in this instance a lead

from a point on the right arm resistor to a point on the left arm resistor which will give a deflection proportional to the horizontal component of the dipole and no deflection in response to its vertical component. It is clear that this can be done whenever the arm electrodes are both strongly negative with respect to the central terminal, for the currents i_b and i_a then have the same sign. If the point on the right arm resistor is separated from the central terminal by the resistance A and that on the left arm resistor is separated from this terminal by the resistance B, the two points will be at the same potential provided Ai_a is equal to Bi_b and this condition can always be fulfilled by choosing the two points properly. In the third case (C), all three electrodes are on the surface of the spherical medium and at the apices of an equilateral triangle. The dipole is at a point on the radius vector to the F electrode at a distance from the center of the sphere equal to one-fourth of its radius. In computing the potentials of the apices of the equilateral triangle in this hypothetical case, we have utilized equations for the field of an eccentric dipole in a spherical medium which were developed by Wilson and Bayley.[6] The Burger triangle is isosceles and of the type in which the side corresponding to Lead I is shorter than those corresponding to Leads II and III. Its shape is, therefore, similar to that of the isosceles triangle of Fig. 5. It does not tell us whether the dipole is centric and the geometric triangle defined by the electrodes therefore identical with it in form, or whether the dipole is eccentric and this geometric triangle equilateral, or isosceles but different from it in shape. The assumption that the dipole is centric leads to the conclusion that the potential of the F electrode for a vertical current axis is 3.47k, whereas its true potential is 4.88k, and that the potential of the central terminal is −0.79k instead of 0.63k which is correct. In summing up this section, we may say that in experiments of the kind under consideration, it is always possible to find one lead which will record only the variations of the horizontal, and another which will record only the variations of the vertical component of the electrical field. It is always theoretically possible to modify the relative magnitude of the resistances in the arms of a central terminal connected to the three limb electrodes in such a way as to insure that its potential will be zero for all positions of the electrical axis, provided that the position of the input electrodes is not one that will make all three lead electrodes simultaneously positive or negative. On the other hand, it is not practically possible to do this unless the true potentials of the limb electrodes are known for two positions of the current axis. It does not appear that this necessary information can be obtained in any way other than by measuring the potentials of these electrodes with reference to that of some point possessing, in respect to the circumscribed region where the current enters the body, "electric" and spatial relations identical with those which it bears to the circumscribed region where the current leaves the body. For some positions of the input electrodes it may be that no point which precisely fulfills the prescribed conditions exists. In that case, it may even be difficult to define in a manner satisfactory to everyone exactly what is meant by zero potential in that particular instance. The concept is one that is derived from the consideration of hypothetical situations for which exact mathematical solutions are available. In practice, the solution of the problem of finding a point at zero

potential represents an approximation to an ideal based on plausible assumptions of one kind or another. We have as yet made no serious attempt in our experiments to measure the potentials of the limb electrodes with respect to that of a point of the kind mentioned, and shall not now discuss this problem further.

In the title of this article, we have referred to the possibility of constructing an Einthoven triangle for a given subject. In order to do this, it would be necessary to be able to generate in the trunk of the given subject an electrical field closely resembling that associated with the heart beat, and to measure the induced potential differences between the limb electrodes for two different positions of the electrical axis. By the method of Burger and Van Milaan, a triangle corresponding to the data thus obtained could then be constructed.

The extent to which the electrical field set up in the body by connecting two electrodes on the precordium to a source of low frequency alternating current resembles the electrical field of the heart is as yet unknown. It may be possible to generate an artificial field in the trunk more like that of the heart by placing small input electrodes in the esophagus or by introducing them into the right ventricle by the catheterization technique. Since the stimulating effect of the current increases rapidly with the current density, the size of the current that could be safely passed into the body by way of the largest input electrodes permissible in such experiments might be inconveniently small, but with a sufficiently sensitive recording system the field produced could undoubtedly be studied satisfactorily. Much information bearing on the problem of generating an artificial field similar to the cardiac field will certainly come from a comparison of the results of experiments on living subjects with those obtained in like experiments on cadavers and on models.

Human chests differ in size and shape and human hearts in location, but we do not as yet have much information concerning the effects of these variations upon the character of the heart's electrical field. In the majority of our experiments in which the point midway between the input electrodes was on the midsternal line and at the level of the fourth intercostal space, the Burger triangle was very nearly isosceles and of the kind in which the side corresponding to Lead I was shorter than the sides corresponding to Leads II and III. In two instances, however, this triangle was of the opposite type. We do not know whether the shape of the triangle obtained was dependent upon the size and shape of the chest or upon some other factor. A larger series of experiments should decide this question.

THREE ISOPOTENTIAL LINES AND THE RECIPROCITY THEOREM OF HELMHOLTZ

In a preceding section of this paper, it was mentioned that we have carried out a very few experiments of a kind suggested by Dr. Kenneth S. Cole, in which two of the limb electrodes are connected to a current source and the isopotential line corresponding to the potential of the third limb electrode is plotted on the body surface. The three lines obtained in this way may be called the right arm isopotential, the left arm isopotential, and the leg isopotential. They intersect at two points, one on the anterior and the other on the posterior surface of the

chest. In the experiments performed thus far, the anterior point has been very close to the midsternal line and usually at the level of the sternal attachment of the fourth costal cartilage or the fourth intercostal space. In the case of one subject, however, it was at the level of the second intercostal space. In the single experiment in which it was located, the posterior point was directly behind the anterior. The isopotential lines found in this instance are shown in Fig. 7.

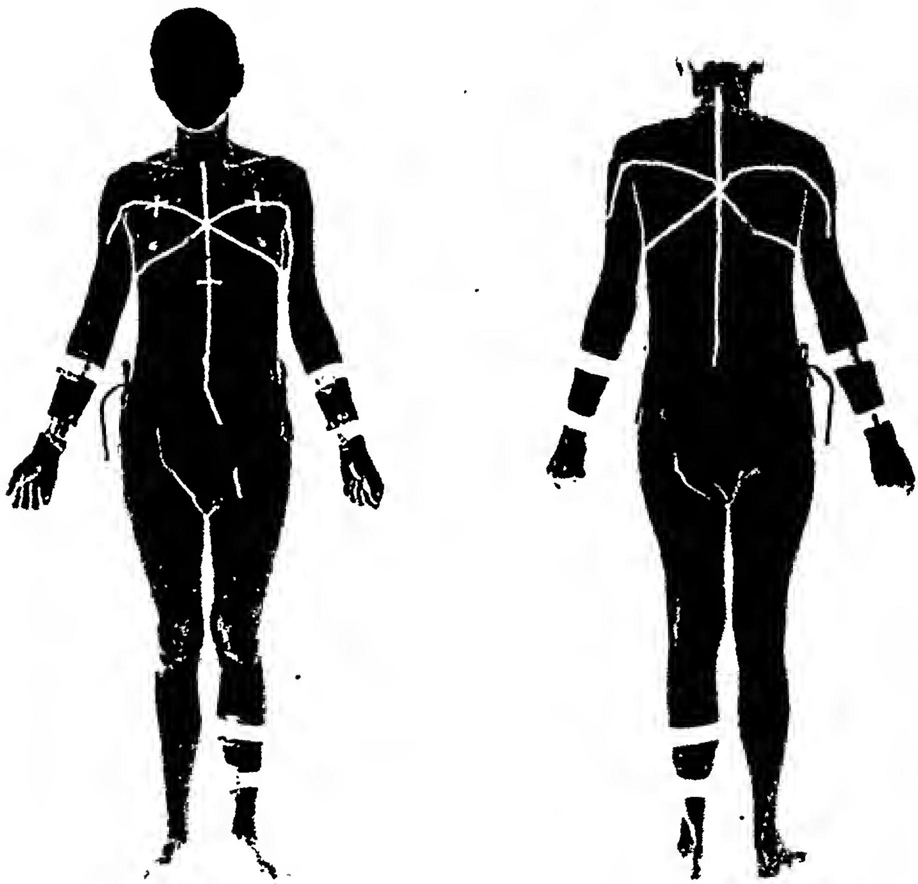


Fig. 7.—Experiment 12. The location of the anterior and posterior intersections of the right arm, left arm, and leg isopotentials.

In Experiment 12, the input electrodes were placed on the leg isopotential at the level required to make the point midway between them and the anterior intersection of the three isopotential lines coincide. The resulting deflection in Lead I was very small and a slight rotation of the input electrodes made it disappear altogether. The wires from the oscillator were then transferred to the electrodes on the arms and the lead wires to the electrodes on the chest. The record obtained again showed no deflection. This procedure was repeated after rotating the current axis through an angle of 90 degrees. This axis was then perpendicular to the leg isopotential and the electrodes were equidistant from it. Under these

circumstances, the deflections recorded were of the same size when the oscillator was connected to the chest electrodes and the lead wires to the limb electrodes as when the reverse was the case (Fig. 8). These observations are in accord with the reciprocity theorem. In 1853, Helmholtz,[7] then a young man 32 years of age, proved this theorem theoretically and experimentally for both homogeneous and heterogeneous volume conductors. We believe that the location of the intersections of the three isopotential lines specified will prove to be a very useful procedure. It promises to disclose significant differences between subjects, and since it requires very little time, a large number can be examined in a relatively short period. It will also make it possible in experiments on different subjects to place the input electrodes in such a manner that their positions, from the electrical point of view, will always be the same with respect to the limb electrodes. What is more important, the principles underlying this procedure and the reciprocity theorem suggest a great variety of experiments which may increase our knowledge of the properties of the body considered as a volume conductor of electrical currents of the kind associated with the heart beat.

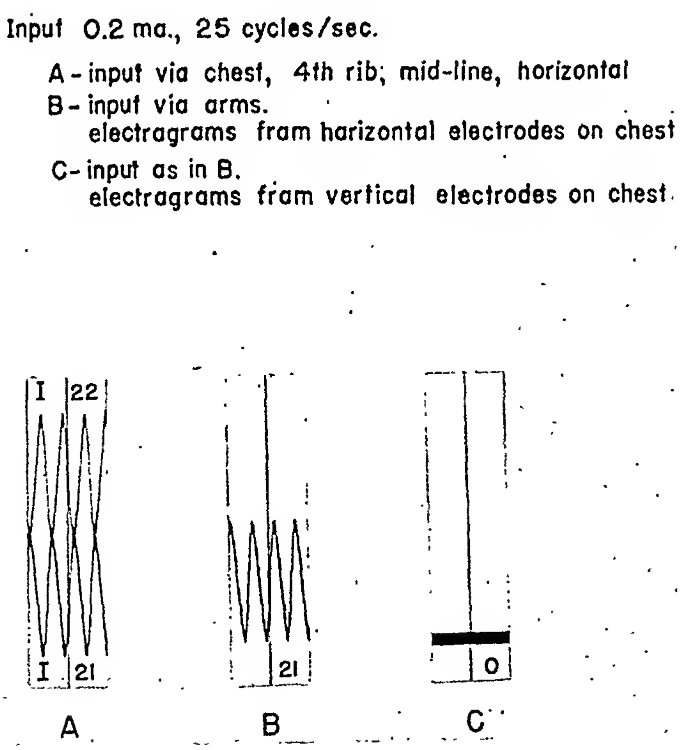


Fig. 8.—Experiment 12. Tracings which illustrate the reciprocity theorem. When there are two electrodes on the limbs and two on the chest, the potential difference between the chest electrodes when the current source was connected to the limb electrodes is equal to the potential difference between the limb electrodes when the current source was connected to the chest electrodes.

THE IMPORTANCE OF THE EFFECTS OF THE POSITION OF THE HEART UPON THE FORM OF THE ELECTROCARDIOGRAM

The ultimate purpose of the work with which this article is concerned is the same as that which led Einthoven and his associates[8] to propose a method of finding the position of the electrical axis of the heart. The first two paragraphs of their famous paper in which this method is described run as follows:

"Die Herzlage beeinflusst die Form des E.K.G. Es ist uns jedoch bei der elektrokardiographischen Untersuchung hauptsächlich darum zu tun, die *Tätigkeit* des Herzens besser zu ermittlen, und man sieht leicht ein, dass, wenn schon durch eine Lageabweichung dieses Organs eine Veränderung in die Form der Kurve hervorgerufen wird, eine Schwierigkeit enstehen muss, um mittels dieser Form auch über die Tätigkeit des Herzens zu urteilen.

Diese Schwierkeit kann am besten gelöst werden, wenn man den Einfluss der Lage vorher genau kennen gelernt hat."

Waller, and many others interested in the electrical aspects of the heart beat, was conscious of this problem long before Einthoven, Fahr, and De Waart attempted to solve it. Today, the differentiation of phenomena produced by displacement or rotation of the heart from those originating within the myocardium itself is still one of the most troublesome of the problems that confront those who attempt to interpret the human electrocardiogram.

There may be little value in computing the exact position of the electrical axis of the heart by Einthoven's method, but there can be no question that the Einthoven triangle has made it possible to recognize with considerable facility peculiarities in the form of the electrocardiogram that result from rotation of the heart about a sagittal axis. The recognition of those peculiarities that result from rotation of the heart about an axis that is not perpendicular to the plane of the limb leads is still extremely difficult. At the same time, our experience with precordial leads has led us to believe that cardiac rotations of this kind are much more often responsible for erroneous interpretations of the electrocardiogram than was formerly suspected. Many changes in the position of the heart that have a profound effect upon the shape of the electrocardiographic deflections cannot at present be recognized by fluoroscopy or by roentgenographic methods. It seems likely, however, that a sound method of taking simultaneously two accurate vectorcardiograms which represent the projections of the cardiac vector upon two different planes and which can be combined to form a spatial curve will contribute heavily to the eventual solution of this important problem. Several methods of this kind have been proposed and some of these have been used to a limited extent. Nevertheless, it has seemed to us that it is desirable to place all methods concerned with the study of the electrical axis of the heart upon a foundation more secure than that upon which they now rest by a thorough experimental study of the distribution in the body of currents similar to those associated with the heart beat. It was with this end in mind that experiments of the kind here reported were undertaken.

SUMMARY

In experiments on normal subjects, two small electrodes on the chest were connected to a source of low frequency current. The resulting differences in potential between the extremities and between other points on the body were measured. By the method described by Burger and Van Milaan, triangles and other figures, which present in graphic form the data obtained in this way, have been constructed.

When the point midway between the input electrodes was in the midsternal line, the triangle corresponding to the standard limb leads was nearly isosceles, and usually, though not always, of the type in which the side corresponding to Lead I was shorter than the other two. When the input electrodes were to the left of the midline, the side of the triangle corresponding to Lead III, and when they were to the right of the midline, the side corresponding to Lead II, was the longest.

When the Burger triangle is oblique, none of the standard or unipolar limb leads yield deflections proportional to either the horizontal or the vertical component of the electrical field. A method of finding two leads, one of which will record the variations of the first of these components, and one which will record the variations of the second, is described. The effect of varying the resistances in the arms of the central terminal upon its potential, and the possibility of reducing the potential variations of this terminal to zero, when the Burger triangle is not equilateral, are discussed.

In a few experiments, the isopotential lines corresponding to the potential of one of the limb electrodes when the other two were connected to a source of low frequency current were plotted on the body surface. The three lines obtained in this way intersect at two points, one on the front and the other on the back of the chest.

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SURGICAL TREATMENT OF HYPERTENSIVE HEART DISEASE AND OF HEART FAILURE OF HYPERTENSION

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During the last few years, extensive surgical resection of sympathetic nerves has been gaining importance in the treatment of so-called essential hypertension. There is enough proof of its immediate efficacy, but its later benefits are still under discussion.

After the purely speculative period of Danielopolu and Pende, who suggested the operation, after the heroic period of the pioneers of the method, Peet, Crile, Adson, and many others, who tried the most varied techniques of rhizotomy, sympathectomy, and ganglionectomy, we clinicians remained skeptical or even distrustful, because of the great number of failures.

In the last six years surgery seems to have improved the technique and to have established a method by which results have turned favorable. Ample intervention, both thoracic and abdominal, such as Smithwick's, with resection of great portions of the sympathetic chain, have produced results which were previously thought to be impossible. Today, everywhere, a great number of hypertensive patients are operated upon. They may not be cured, but their blood pressures are lowered and their symptoms at least are improved. Perhaps fatal complications are eliminated or delayed. In any event, operation makes many hypertensive patients capable of returning to normal life and activity.

It is a sure fact that surgical treatment lowers high blood pressure considerably in the majority of cases and that improvement usually lasts for long periods of time. As a natural consequence the excessive strain on the heart is reduced proportionately. Nevertheless, it is wise to review the problem with a critical spirit in order to determine whether surgical intervention is the proper way in which to cure heart failure which is so often a complication in hypertension.

Let us then review the possibilities offered by surgical treatment. It is accepted that patients whose hypertension is slight and responds to medical treatment present no particular problem and are not to be considered for surgery. The problem arises with patients in whom the blood pressure, particularly the diastolic, is very high and in whom medical treatment has proved inefficacious, and particularly with patients in whom severe complications are to be expected.

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This is equivalent to the statement that surgical treatment is limited to the group of patients with severe hypertension. But even in this group selection must be made. Severe arterial degeneration makes improvement after surgery improbable. The same has been said regarding advanced visceral complications, cardiac or renal, especially if these complications have produced organic insufficiency. Likewise, recent cerebral thrombosis or hemorrhage has, up to now, placed a patient beyond the benefit of surgery.

If patients with slight hypertension are eliminated and those with advanced or complicated disease are discarded and surgical treatment, therefore, is limited to an intermediate group in whom intervention can be predicted to be of value, even then a selection of suitable patients is necessary. Considering that the neurogenic factor is the main cause of sustained vascular spasm, numerous tests have been devised to measure and eliminate this factor. There are a number of such tests, among them those that depend upon the response to Amytal, Pentothal, Etamon, and other substances. In spite of the apparent soundness of the reasoning which suggested these tests, experience has proved that such tests are often misleading. We have all been disappointed with the results obtained in patients with strongly positive tests who did not obtain the benefit expected from the sympathetic denervation. Conversely, we have all had patients in whom a poor result was expected after operation because of negative tests, and yet in whom a great reduction of blood pressure occurred. On this point opinion tends to be uniform; the tests proposed up to the present time are absolutely uncertain and cannot be relied upon in the selection of patients.

Objective tests do not furnish a sound basis for the selection of hypertensive patients suitable for surgery, in our opinion. The method we follow is a simpler one. It consists simply in recommending operation to those patients who need it, so long as there is no positive contraindication. This method requires only that one know which hypertensive patients are in need of surgical treatment and what conditions and circumstances positively contraindicate surgery. Numerous combinations of factors may be present and may make the clinical picture an apparently complex one. We believe that the problem of selection may be simplified by dividing the patients with essential hypertension into four groups according to the importance of their disturbance and the stage of their disease.

Group 1.—This group is made up of those patients with slight or moderate hypertension which has not produced vascular or visceral complications. Evidently these patients are not in need of the operation. Medical treatment only is indicated.

Group 2.—This group is composed of patients with severe hypertension, especially diastolic, who have not yet shown any important complications. Patients in this group have no vascular sclerosis or, at most, incipient sclerosis, their hearts are normal, their eye grounds fit into Type I or even II of Wagener and Keith's classification, and, finally, their renal function tests are normal. This group of patients is the one considered, in principle, as ideal for surgical treatment. Indeed, it is the group in which expectation of success is greatest and the risks slight. In practice, however, patients in this group very often do not accept

the recommended operation; moreover, the physician on his part does not feel justified in strongly urging a resort to surgery. When there is as yet no complication, it is not easy always to convince a patient to face an immediate risk in order to avoid a future danger. Surgical indication, at least in our experience, is somewhat illusory in this group of patients with uncomplicated hypertension.

Group 3.—This group includes patients who have severe hypertension and who show definite evidence of visceral complication, although these complications are not yet advanced. In the majority of patients there is present definite hypertensive heart disease with cardiac enlargement and even a gallop rhythm and an abnormal electrocardiogram. In some patients in this group, the evidences of cardiac strain may not be so marked, yet there may be evidence of encephalopathy (Grade 3 eye ground changes) or evidence of early renal sclerosis. In patients who fall into Group 3, although there is present easily recognizable structural damage, there does not yet exist functional insufficiency of an advanced nature.

Patients in this group have been generally considered as undesirable for surgery. Arteriosclerosis and structural visceral involvement which these patients show have been regarded as irreversible and as contraindications for operation. There is a mistake in this conception, at least in so far as it concerns those with cardiac complications. Limiting our consideration to these, we may say that, save for those in whom very special reasons exist, it is the patients in this group who most urgently need surgical intervention. Possibly brain and kidney damage is not likely to regress, but the same is not true of the heart. In cardiac damage, the most frequent complication, the physician may feel perfectly justified in insisting upon operation, and the patient, who is already confronted with the already existing ominous risk, may well accept the lesser risk of surgical treatment.

It is true that anatomical damage is already present in the heart, but when this is of slight degree, it is in a way reversible when the hypertension is corrected. On the other hand, since cardiac damage is not yet severe, it does not add to the risk of the operation. The onset of heart damage is a call for help. Since medical treatment is incapable of suppressing the cause, surgical intervention is the only means available for giving help to the strained heart.

Opinions already expressed by others give some support to the recommendations that are being made. White[10] states categorically that hypertensive heart disease "is more an indication of the necessity of operation than a contraindication as was previously thought." Allen[1] is less categoric and he limits his statement by saying that "albuminuria and moderate heart enlargement do not constitute a contraindication." Peet and Isberg[7] maintain that "heart enlargement and an abnormal electrocardiogram are not a contraindication for operation."

To support the opinion that patients with elevated blood pressure and with definite cardiac change should be operated upon before they develop functional cardiac insufficiency, we have carefully studied and followed a series of patients. The results confirm this opinion. Very recently, Isberg and Peet[5] presented a large survey of 275 patients with hypertensive heart disease, 60 per cent of whom

are living five to thirteen years after operation; in this series intervention was more efficacious in patients with less advanced disease.

Group 4.—This group includes patients with more advanced hypertensive disease, who have severe visceral complications consisting of heart failure, renal insufficiency, or severe encephalopathy.

Opinions have been unanimous for a long time that patients who belong in this group should not be operated upon. Summarizing the experience at the Mayo Clinic, Allen maintains that it is useless to operate upon a patient who has had heart failure, auricular fibrillation, angina pectoris, severe renal insufficiency, or high grade hypertensive encephalopathy. Peet and Isberg[7] agree with this view and state that "in these cases, lasting benefit is seldom attained." Padilla and Cossio[6] report only temporary improvement in five patients with heart failure who were operated upon, and for this reason they are not in favor of surgical treatment in this type of patient.

Yet, even in this group of patients, it seems that such a positive decision should be modified, at least for those patients in whom heart failure constitutes a major disability. In the same way that the patients in the previous group, who were formerly rejected, are now known to be amenable to surgery, so the patients in this group are subject to benefit from operation.

Considering the problem fundamentally in terms of the heart and not of cerebral and renal complications, since the latter lesions do not have the same tendency to regression that exist in cardiac lesions, it is conceivable that the mechanical factor of overwork and strain plays a decisive role in producing and later maintaining heart failure. It is true that in the genesis of heart failure there is another factor besides the mechanical one: that of coronary sclerosis with defective myocardial blood supply. Nevertheless, without the excessive work originated by the high pressures, there would not be failure and the damage to the coronary arteries would be stopped or at least delayed.

No form of therapy for the heart failure of the hypertensive patient is logical unless it lowers the blood pressure. Rest and digitalis therapy, which have constituted our only means of treating these patients up to this time, have only temporary efficacy. As long as hypertension, that factor which fatigues and strains the heart, continues to act, relapses are inevitable, and with each relapse the damage to the heart becomes more severe.

Up to the present, only White[10] has supported the view that a certain degree of heart failure, if not advanced, is amenable to surgical treatment. Isberg and Peet,[5] on their part, have recently modified somewhat their earlier sceptical attitude: In sixteen operated patients with heart failure they report a survival of over five years in five patients. In view of this fact, they maintain that resort to surgical intervention "should not be denied once the patient is properly digitalized."

We, on our part, have been forced to go farther and to try surgical intervention in patients with desperate grades of hypertension who have developed severe heart failure, even when the failure is intractable and resistant to digitalis treatment. Our experience offers legitimate hope. We shall summarize the results in our first case, which justifies this heterodox opinion.

In April, 1945, one of us (I. C.) recommended Smithwick's operation to a 50-year-old business man, a very nervous individual with severe hypertension who had been under treatment for two years. In the beginning his blood pressure was around 250/150 and could not be lowered by the usual medical treatment, including thiocyanate. Later, heart enlargement developed, and then heart failure with presystolic gallop rhythm and visceral congestion appeared, both rapidly subsiding with rest and ouabain. Still later, repeated relapses occurred. With these relapses there were alarming paroxysms of nocturnal dyspnea and diastolic hypertension up to 160 mm. of mercury. Medical treatment gradually became ineffective, digitalis and ouabain lost their efficacy; and the patient spent night after night in tormenting asphyxia.

When the situation became intolerable and medical treatment had nothing to offer, the patient accepted operation, knowing the great risk involved. Medical treatment was redoubled until the patient was brought into the best possible condition. Dr. Clemente Robles performed the operation at the Institute in April, 1945.

After a tormented postoperative period, evident improvement followed. Hypertension was reduced from 220/160 to 190/110 in the recumbent position and 170/110 in the standing position; heart failure soon subsided and disappeared in the course of two months; the electrocardiogram was favorably modified though it did not become normal; the eye grounds did not change. Against medical advice, the patient returned to a normal, active business life four months after operation. At the present time, three years after operation, he is traveling through Europe in very good condition. The patient apparently presented a definite contraindication to surgery. The results proved that there are no absolute contraindications.

As a result of the experience gained from this patient, we have subjected to operation ten additional patients in the Institute of Cardiology, all of whom had hypertensive heart disease and heart failure of variable degrees. The results are summarized in Table I.

In the total of eleven patients there has only been one death which can be attributed directly to surgery; and another fatality should be judged with certain reservation. Death in the first patient was due to a cerebral hemorrhage eleven days after operation. Death in the second patient occurred the day after operation and was due to occlusion of the aqueduct of Sylvius by a fibrinous thrombus: the existence of an old meningitis had been overlooked. A third patient died ten months after operation; death was due to the natural progress of his disease and to the development of uremia. The other eight patients were cured of their heart failure and they have not relapsed after follow-up periods ranging from one to three years. Almost every patient has resumed a normal life and the blood pressure is only slightly elevated, if not normal.

This small group is impressive if one considers that it is made up of patients with the most severe grade of hypertensive heart disease with heart failure: a type of patient who was previously rejected from surgery. It is impressive also because of the unexpected proportion of successes: 75 per cent.

TABLE I. RESULTS OF SYMPATHECTOMY IN ELEVEN PATIENTS WITH HYPERTENSIVE HEART DISEASE AND HEART FAILURE

NO.	AGE (YEARS)	BLOOD PRESSURE BEFORE OPERATION	BLOOD PRESSURE AFTER OPERATION		HEART ENLARGEMENT	HEART FAILURE	RECOVERY FROM HEART FAILURE	FOLLOW-UP PERIOD (YEARS)
			RECUMBENT	STANDING				
1	50	240/140	180/120	160/110	++	++++	Complete recovery	3
2	35	185/155	170/120	130/90	+++	+++	Complete recovery	2½
3	41	185/115	170/100	140/80	++	++	Complete recovery	2
4	50	250/130	180/110	150/100	+	++	Improvement	2
5	61	180/110	160/100		+	+	Considerable improvement	2
6	46	210/110	220/110	170/100	++	+++	Slight improvement	2
7	38	200/130	170/110	170/100	+	++	Considerable improvement	1½
8	29	230/150	170/80	160/80	++	+	Considerable improvement	1½
9	36	260/160	200/120	200/120	+++	++++	Death 10 months after operation (uremia)	
10	57	200/140	—	—	+++	+++	Death 11 days after operation (cerebral hemorrhage)	
11	51	210/140	140/110	—	++	++	Death the day following operation (occlusion aqueduct of Sylvius)	

The barrier which formerly barred from surgery patients classified as Group 3, hypertensive patients with secondary heart disease, has been pushed back gradually in the last six years. Now only patients who fall into Group 4, that is, hypertensive patients with heart failure, are deprived of sympathetic surgery.

On the basis of the results presented today, it is seen that this limitation is not always justified. We do not intend, of course, to advocate surgical treatment for all patients with hypertensive heart disease which has reached the final stage of heart failure, but there are times when it is better to disregard the apparent contraindications. Since there is no effective medical treatment for lowering the blood pressure, surgery is the only form of treatment capable of giving relief to the heart when rest and digitalis have lost their effectiveness. In support of this view, we offer this group of hypertensive patients in the final stage of heart failure, at times of advanced nature, who have been treated surgically with success.

We admit that the operative indication which we have discussed is simply an indication in principle. Our recommendation of surgery is made broadly. A number of added factors must be considered and their presence may clearly contraindicate surgery. These factors are chiefly advanced damage to the coronary arteries and advanced myocardial degeneration. Only such considerations as the careful evaluation of these factors, of the existing visceral complications, and of the resistance of the patient to operation will permit the physician to decide in each case whether surgical intervention is indicated or not. In advanced cases of hypertensive heart disease in which the heart is greatly enlarged, the coronary arteries are severely damaged, and heart failure is long standing, operation is clearly contraindicated. In moderate cases, on the contrary, it is probable that the treatment will have to be both medical and surgical in the future.

SUMMARY AND CONCLUSIONS

In the surgical treatment of arterial hypertension by means of sympathetic denervation, it has been considered up to the present time that hypertensive heart disease and especially heart failure were formal contraindication to operative procedure. Unfortunately, patients with these handicaps are precisely the ones who most urgently need lowering of their blood pressure.

When medical treatment has failed we have been forced at the Instituto Nacional de Cardiologia to operate upon a number of hypertensive cardiac patients, all of whom were in heart failure which in some was of extreme degree.

Of the eleven patients operated upon, one died from cerebral hemorrhage eleven days after operation; another succumbed the day after the operation from occlusion of the aqueduct of Sylvius, the result of an overlooked old meningitis; a third patient died ten months after operation in uremia.

The other eight patients improved ostensibly and for a long time; they are still alive after one and one-half to three years and have shown no evidence of heart failure since operation. Some of them have resumed normal life.

We feel that instead of being a contraindication, hypertensive heart disease is fundamentally a formal indication for surgical treatment as the only means of staying myocardial damage.

We believe furthermore that heart failure, when it is not accompanied by very advanced lesions, may sometimes be corrected through the operative procedure, even in protracted cases where digitalis and ouabain have failed.

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THE CORONARY VASODILATOR ACTION OF KHELLIN

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OUR interest in Ammi Visnaga and its active principle, "khellin," arose as a result of an accidental observation. For the last three years a member of our laboratory staff has been suffering from definite symptoms of coronary insufficiency. Anginal attacks were frequent; they occurred not only after exertion but also spontaneously, especially after meals, and sometimes even at night. In addition to his coronary complaint, the man became a victim of renal colic of such severity that he had to stop his work. X-ray examination revealed the presence of three calculi in the left ureter. After taking various remedies without much benefit, he was advised to try a tincture of Ammi Visnaga. This apparently was of some help; at any rate, on the seventh day he passed some sand and a calculus. At the time we were not aware of his condition and our attention was drawn to him only after his return to work. The man, who usually behaved like a semiinvalid, appeared stronger and more vigorous; he moved faster, lost his apprehensive and frightened look, and could climb the staircase without the usual attacks. He said that he was free from attacks also during the rest of the day. He attributed his improvement to the passage of the calculus, which, however, proved to be wrong since a few days later his general condition became as bad as before. On investigation we found that during the period of colic the man consumed up to 20 c.c. of tincture of Ammi Visnaga per day. On the off chance that visnaga was the cause of his temporary improvement, we persuaded him to repeat the treatment. The relief which followed was so unmistakable that he has continued to take the drug for over two years.

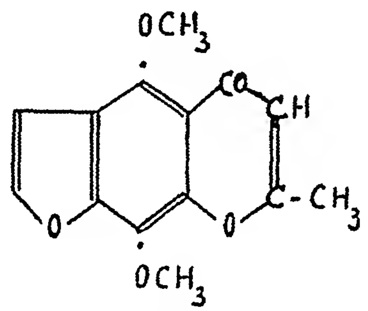
As a result of this observation we decided to investigate the action of Ammi Visnaga on the cardiovascular system with special reference to the coronary blood flow and the heart muscle.

The considerable amount of experimental and clinical observation which has at present accumulated gives a sufficiently sound foundation for a comprehensive review of the therapeutic value of the various crystalline principles which have been extracted from the fruit of Ammi Visnaga. This plant, known in Arabic as "Khella," grows wild in the Eastern Mediterranean countries. The local population has been using decoctions of its seeds as an antispasmodic since ancient times.

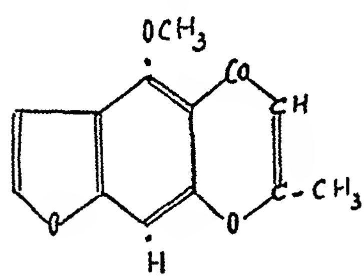
From the Physiological Laboratory and Fouad I University Hospital, Kasr-El-Aini, Cairo, Egypt.
Presented before the Third Inter-American Cardiological Congress, Chicago, Ill., June 13-17, 1948.
Khellin was supplied by the Alpha Laboratories, Cairo, in the form of *Ammicardine*.

So far, three distinct crystalline substances have been extracted and isolated from the seeds in a pure form. The three substances, the molecular and structural formulas of which have been determined, are as follows:

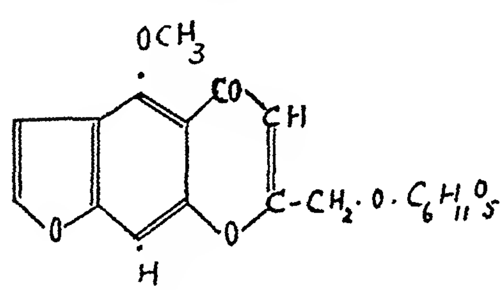
1. Khellin: This substance was first prepared in an impure form by Mustapha[1] in 1879, who also suggested the name, and again by Malosse[2] in 1881. Fantl and Salem[3] in 1930 isolated pure khellin, determined its composition, and suggested a structural formula which was somewhat modified subsequently by Spaeth and Gruber[4] in 1938. Chemically, khellin is a dimethoxy-methyl-furano chromone (Fig. 1).



I Khellin.



II Visnagin



III Khellol-glucoside.

Fig. 1.—The structural formulae of the substances the biological action of which is described in this communication.

2. Visnagin: This substance was first isolated by Spaeth and Gruber[5] in 1941, who found it to be a monomethoxy-methyl-furano chromone (Fig. 1). Visnagin is found in the seeds in negligible amounts.

3. Khellol-glucoside: This substance was first isolated and named by Fantl and Salem[3] in 1930. The structural formula of this substance was determined by Spaeth and Gruber[6] in 1941, according to whom it is an oxyglucoside of visnagin (Fig. 1). Khellin and the glucoside are found in the dried seeds in approximately equal amounts.

In 1931 the pharmacognosical features of the two main crystalline substances were studied by Fahmy[7,8] and in 1934 the decoction and the tincture of Ammi Visnaga were included in the Egyptian pharmacopeia. Samaan in 1932 investigated the biologic action of khellin[9] and of the glucoside[10] which he called, respectively, "visamin" and "khellinin." We prefer to use the names originally given to these substances by the workers who first isolated and analyzed them. Furthermore, the original nomenclature has been widely used in the German and English literature. The name "visamin" seems to us unsuitable also because it might imply the presence of an amino group, which is not the case.

According to Samaan,[9] khellin causes a relaxation of all the visceral smooth muscles, while the glucoside has no special action. No further investigation of these substances seems to have been made until Anrep, Barsoum, Kenawy, and Misrahy[11] demonstrated that khellin causes a conspicuous dilatation of the coronary blood vessels. The minimal effective concentration of the drug causing definite coronary vasodilation in the heart-lung preparation in dogs was found to be of the order of 10^{-6} which is considerably smaller than for aminophyllin and other xanthine derivatives. With concentrations of 10^{-5} the coronary sinus outflow increases up to three times the initial volume. The action of khellin, although very considerable, is less than that of amyl nitrite, but it has the advantage of being much more prolonged. Gradual administration of khellin up to concentrations of 10^{-4} has no undesirable effect on the heart muscle, on respiration, or on the general blood pressure. Rapid intravenous injections of large doses of khellin cause a temporary drop of the blood pressure; but no such effect was ever observed when the drug was injected slowly into the veins or administered intramuscularly. It was further found by Anrep, Barsoum, and Kenawy[12,13] and later by Bagoury[14] that in somewhat larger doses khellin causes coronary dilatation also in the isolated perfused rabbit heart and that it relaxes the bronchial musculature of the guinea pig even after an artificially induced spasm caused by the administration of histamine. Administration of concentrated solutions of khellin, as happens when the drug is injected into the cannula perfusing the isolated heart, weakens the heart muscle. The drug should be administered in very dilute solutions. No such weakening was observed in the blood-perfused heart-lung preparation. Fig. 2 is a graphic representation of the effect of khellin on the coronary sinus outflow in the heart-lung preparation.

Similar results were also obtained in experiments made on the whole animal after its blood was rendered uncoagulable with a mixture of heparin and chlorazol fast pink.

The observation of Samaan[9] that khellin causes a relaxation of the intestinal musculature was confirmed on the isolated intestine and in the whole animal. Methods were devised for the biological assay of khellin in the blood

and the tissues, and the colorimetric method first suggested for this purpose by Fahmy was improved by Anrep, Kenawy, Barsoum, and Fahmy.[15] The improvements in the assay of khellin allowed us to study the rate of its absorption and to determine its concentration in the blood and tissue at different periods of time after administration of the drug.

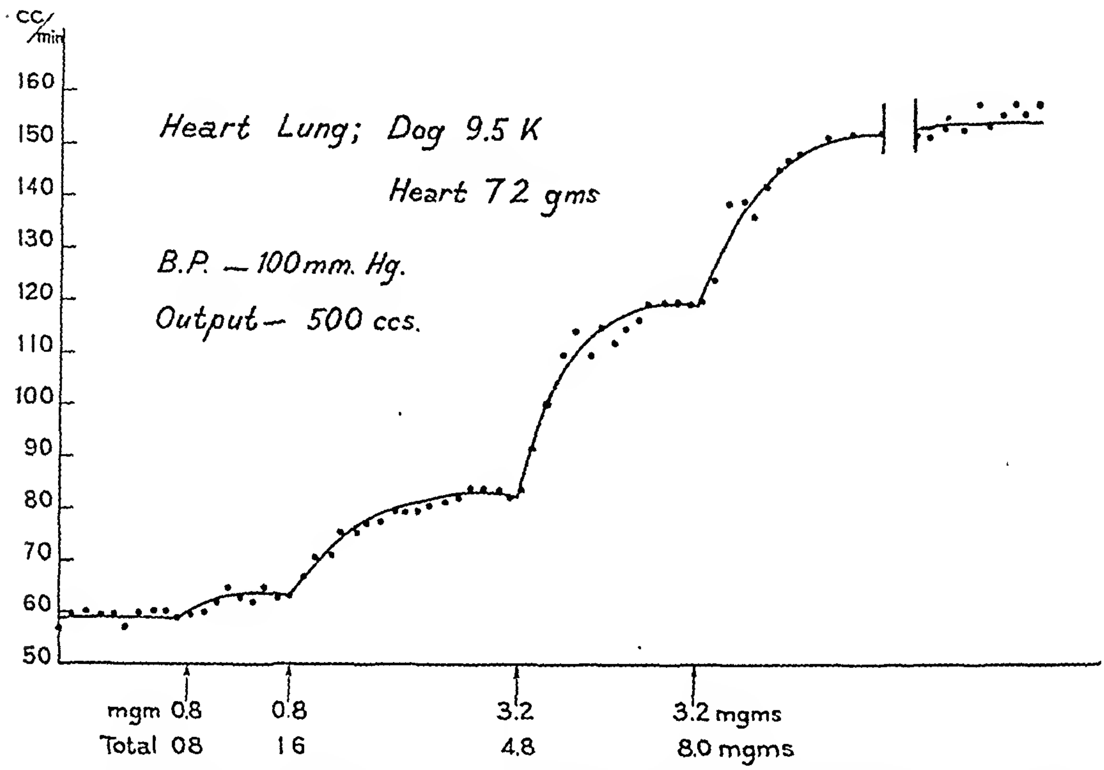


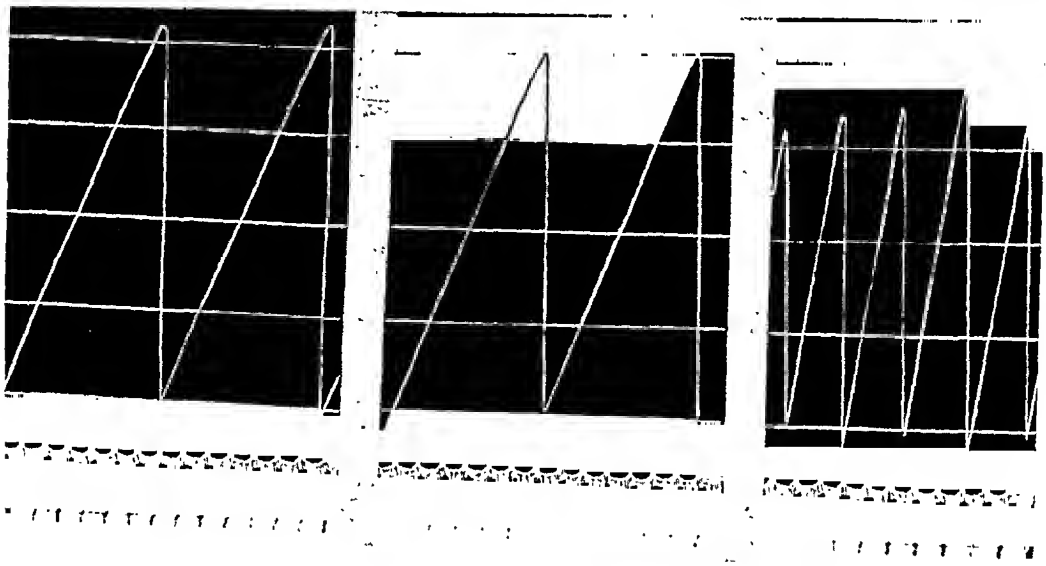
Fig. 2.—The coronary vasodilator action of khellin as measured by the sinus outflow of blood in the heart-lung preparation. The total amount of blood in the circulation was about 900 cubic centimeters. The gap in the curve corresponds to an interval of twenty minutes. The drug was administered into the venous reservoir of the apparatus.

Intramuscularly administered, khellin is rapidly absorbed[16] into the circulating blood, reaching a maximal concentration in five to seven minutes. It is also rapidly absorbed from the stomach and from the small and the large intestines, the maximal concentration in the blood being reached in ten to fifteen minutes. After absorption, khellin becomes approximately uniformly distributed in all the tissues and organs of the body, a fact which has to be taken into consideration in the calculation of the effective dose to be administered. The destruction and excretion of khellin after it has been absorbed is slow. After an interval of twenty-four hours its concentration in the tissues is approximately halved and traces of the drug can be found in the blood and tissues as late as four days after its administration. The concentration of the drug in the blood does not diminish more rapidly than in the tissues, which indicates that the latter serve to store the active principle. This also explains the prolonged action of the drug.

Because of the prolonged retention of khellin in the body, repeated administrations of the drug have a cumulative effect. The saturation of the organism

with the drug gradually increases. For example, thirty minutes after the first intramuscular injection of 200 mg. of khellin in man, its concentration in the blood was 4 to 6 μg. per cubic centimeter; after five further similar injections, one per day, the concentration of khellin in the blood rose to 15 μg. per cubic centimeter. Five days after the last injection the blood of the subjects still contained about 2.5 μg. per cubic centimeter.

Experiments with the khellol-glucoside[15] gave completely negative results. This substance causes no relaxation of the smooth muscles and no coronary vasodilation (see Fig. 3). Furthermore, it was shown that the glucoside is not changed in the body into the active khellin and that, in fact, the glucoside is not even absorbed from the gastrointestinal tract. We consider, therefore, that the glucoside presents no therapeutic interest.



A. B. C.

Fig. 3.—Heart-lung preparation. Top tracing is the coronary blood flow as measured by a volume recorder. The horizontal lines are graduations of 10 c.c. each.

The middle tracing is the blood pressure in mm. Hg and the bottom tracing is time in ten-second intervals. Mean systemic arterial blood pressure was 120 mm. Hg.

A, Normal coronary blood flow (55 c.c. per minute).

B, Coronary blood flow after injection of 100 mg. of the glucoside (55 c.c. per minute).

C, Coronary blood flow after injection of 10 mg. of khellin (145 c.c. per minute).

With regard to the third crystalline principle of Ammi Visnaga, namely, visnagin, its biologic action is similar to that of khellin except that it is about 30 per cent weaker. It occurs in the seeds in such small quantities that it presents no special interest. It is also rather difficult to separate visnagin from khellin since both are soluble in the same solvents, which is not the case with the glucoside which, therefore, can be removed easily from the extracts.

The action of khellin on the systemic blood vessels and, therefore, on systemic blood pressure can be completely discounted when therapeutic doses are used. The concentration of the drug must exceed all reasonable limits to cause a

relaxation of the systemic blood vessels. In this respect one can consider the action of khellin on the coronary blood vessels, as nearly as possible, a selective one.

The kidney function is not impaired by prolonged administration of the drug. The old view that khellin causes a diuresis could, however, not be confirmed by Salama[17] in 1946.

As stated before, the value of the decoctions of Ammi Visnaga as an antispasmodic has been realized since ancient times; it has not, however, been used until recently except in cases of ureteral spasm to help the passage of ureteral calculi. The experimental findings summarized here open at least three new lines of investigation, namely, the use of khellin in the treatment of the anginal syndrome, the treatment of bronchospasm, and the treatment of gastrointestinal spasm and also the spasm accompanying gastroduodenal ulceration. The results of our observations upon bronchial asthma and the gastrointestinal tract at present are in preparation for the press; the rest of this communication is devoted to the treatment of the anginal syndrome.

COMPARISON BETWEEN KHELLIN AND AMINOPHYLLIN

A series of comparative observations were made upon the action of khellin and that of aminophyllin on the coronary circulation and on smooth muscle. The action of khellin on the bronchi of the guinea pig was found to be about four times stronger than that of aminophyllin, while when tested on the rectal caecum of the fowl,[18] khellin was twelve times more effective than aminophyllin.

The comparison of the coronary vasodilator action of the two drugs was made on the heart-lung preparation and on the isolated rabbit heart. For obvious reasons, the testing of the two drugs could not be made on the same heart-lung preparation. Therefore, the action was studied on two separate preparations, the separate studies being done as nearly as possible under the same experimental conditions. The type and weight of the dogs used for the two preparations was the same; the arterial blood pressure, the temperature, and the cardiac output, as well as the total amount of blood in the circulation, were kept the same and the two hearts usually did not differ in weight by more than 5 grams. In spite of the limitations imposed by such a method of comparison, the difference in the action of khellin and of aminophyllin was unmistakable. The following comparative experiment serves as an example.

In the first heart-lung preparation the coronary sinus outflow increased after administration of 10 mg. of khellin from 41 c.c. per minute to 120 c.c. per minute. In the second preparation the outflow was 36 c.c. per minute before and 39 to 40 c.c. per minute after administration of 20 mg. of aminophyllin; after a second dose of 20 mg. the outflow increased to 84 c.c., and after a third similar dose, to 125 c.c. per minute.

On the basis of other similar experiments, as well as experiments in which the blood flow was measured in the left coronary artery, we conclude that khellin is at least four times more effective as a coronary dilator than aminophyllin.

Observations on the isolated rabbit heart present the advantage that the two drugs can be administered in succession in the same heart. It must be

remembered, however, that the rabbit heart is less sensitive than the blood-perfused heart in the heart-lung preparation. The following experiment serves as an illustration of the results obtained by this method.

The rabbit heart was perfused with oxygenated Ringer-Lock solution through a three-way cannula which could be alternately connected to a reservoir containing a normal solution, to another reservoir containing khellin, or to a third reservoir containing aminophyllin. The perfusion pressure was kept at 120 mm. Hg and the temperature at 38° centigrade. The results are shown in Table I.

TABLE I. COMPARISON OF EFFECTS OF KHELLIN AND AMINOPHYLLIN UPON CORONARY BLOOD FLOW IN THE ISOLATED PERFUSED RABBIT HEART

PERFUSING SOLUTION	CORONARY OUTFLOW IN C.C. PER MINUTE, MEASURED AT MINUTE INTERVALS
Ringer-Lock	7.6, 7.4, 7.5, 7.6, 7.4
R-L solution plus 10 μg./c.c. of khellin	7.6, 8.5, 10.2, 13.4, 14.0, 14.2, 14.1, 14.2
Ringer-Lock	14.0, 13.2, 12.0, 10.6, 8.3, 7.7, 7.2, 6.9, 7.3
R-L solution plus 30 μg./c.c. aminophyllin	7.3, 7.7, 8.7, 9.1, 8.8, 8.6, 8.7, 9.0, 8.8
R-L solution plus 40 μg./c.c. aminophyllin	9.5, 10.2, 11.1, 13.6, 12.9, 13.3, 13.6
After perfusion with normal Ringer-Lock solution the coronary outflow returned to an average of 6.0 c.c. per minute when khellin was administered for a second time.	
R-L solution plus 10 μg./c.c. khellin	6.0, 6.9, 7.9, 10.2, 11.7, 12.1, 13.2, 13.0

The experiments upon the isolated heart thus confirm the results obtained on the heart-lung preparation. The action of khellin is thus about four times stronger than that of aminophyllin.

TREATMENT OF CORONARY ARTERY DISEASE

Khellin was clinically tried on 300 patients suffering from coronary artery disease. The cases fall into two groups: (1) 250 patients with angina of effort or decubitus; (2) 50 patients with coronary thrombosis, with or without anginal attacks during the period of absolute recumbency.

Khellin was used either as a continuous treatment to prevent or diminish the number of attacks or occasionally for the relief of the actual attacks. The subjective effects of the drug were recorded in every case. Most of our patients were more or less stable and knew the amount of exercise which would evoke an attack. Most of them had been treated previously with other coronary vaso-dilator drugs such as aminophyllin and theophyllin. Objective tests were carried out on some of the patients by registration of the electrocardiographic changes caused by graded exercise before and after administration of khellin. Controlled exercise tolerance tests were made whenever the condition of the patient allowed. Patients giving a history of a recent coronary thrombosis or showing any signs of myocardial failure were exempted from these tests. To eliminate any possible interference of a psychic element in the action of the new drug, placebos were

administered either in the form of injections or tablets containing no khellin, or, without the patient's being informed, the dose of khellin was suddenly reduced. No other drugs were given during the treatment except, when necessary, an occasional trinitrin tablet to some of the patients.

Method of Administration.—Khellin was administered in the following forms: (a) As a purified liquid extract containing 50 mg. of the active principle per cubic centimeter. The dose is 1.0 to 2.0 c.c. diluted with water. This preparation has a bitter taste and should be taken preferably with meals. (b) As tablets, each containing 50 mg. of khellin; one to two tablets are to be taken after meals. (c) As intramuscular injections in a strength of 50 mg. per cubic centimeter; 2 c.c. are injected once or twice daily and during anginal attacks. The injection causes a slight local pain which lasts a few seconds.

In most of our cases, the tablets or liquid extract were used, but in severe cases a combined treatment using injections as well as oral therapy was resorted to. The minimal effective daily dosage was calculated as 2.0 mg. per kilogram of body weight.

Results in Patients With Angina Pectoris.—

Our preliminary clinical trials of khellin were published in 1945 and 1946.[19,20] The results were encouraging and justified further investigation. Reports confirming our results have been published by Ayad.[21] The 250 patients comprising the group with angina pectoris were subjected to khellin treatment. The cases were divided into three classes according to the severity of the condition. Eighty patients were classed as being mild cases, 115 as moderate, and fifty-five as severe. The group comprised 225 men and twenty-five women and their ages varied between 35 and 76 years. The duration of the anginal symptoms was between three and fifteen years in 168 cases, between one and three years in fifty-two cases, and less than one year in thirty cases. Hypertension was present in eighty-four cases and diabetes mellitus in eighteen. The Wassermann reaction was negative in all except three patients. The electrocardiogram was abnormal in 102 cases and the heart was hypertrophied in fifty-nine cases. In eighteen cases the anginal symptoms appeared after an attack of coronary thrombosis.

Response to Treatment: The response to khellin was arbitrarily classed as good, moderate, or negative; good when the anginal attacks ceased altogether or became very infrequent and mild, moderate when they diminished in frequency and severity, and negative when no favorable change occurred. On this basis the results are summarized in Table II. The duration of observation and treatment varied from three months to two years, being eight months or longer in two-thirds of the cases, excluding those classed as failures.

Continuous Treatment: Oral treatment was given to most patients, except when a response was delayed or the case was severe. Under these conditions combined oral and parenteral treatment was used in order to produce a high level of khellin in the blood. Response to treatment occurred after three to five days in mild and moderate cases and after seven to ten days in severe cases. Optimal

improvement is always expected after two weeks' treatment. As previously stated, the drug is cumulative and is slowly excreted from the body. When improvement is obtained, a maintenance dose of 50 to 100 mg. or even more, according to the severity of the case, can be given for many months or even years without any untoward effects.

TABLE II. THE RESPONSE TO KHELLIN OF 250 PATIENTS WITH ANGINA PECTORIS

GRADE OF ANGINAL PAIN	RESPONSE TO TREATMENT		
	GOOD	MODERATE	NEGATIVE
Mild	68	12	—
Moderate	56	55	4
Severe	16	18	21
Total	140	85	25
Percentage	56	34	10

It can be seen from Table II that 56 per cent of the patients showed good improvement, 34 per cent showed moderate improvement, and 10 per cent failed to respond. If the drug was discontinued for a few days or replaced by a placebo, the attacks reappeared, sometimes in a milder form. No habituation to the drug was ever noticed during our investigations.

Treatment of Individual Attacks: The liquid extract was given to patients during the attacks, and relief was obtained in more than 70 per cent of the cases. In the case of more prolonged attacks, intramuscular injections of 100 mg. brought relief in a few minutes. On the whole, the relief obtained was slower than after trinitrin tablets.

Objective Tests: Some of the patients were subjected to standardized exercise tolerance tests by stepping on a chair 40 cm. high at the rate of thirty times per minute. Electrocardiograms were taken before and after the exercise. The exercise was continued until the patient felt definite precordial pain. A few hours later or on the next day, the same exercise was performed thirty minutes after an intramuscular injection of 100 mg. of khellin and the electrocardiogram was again recorded. The RS-T depression and T-wave inversion occurring after the exercise test were prevented by khellin administration. In some cases the same test was repeated after one or two weeks' continuous treatment. In all patients tested, the exercise tolerance increased after khellin. Fig. 4 is an example illustrating the effect of khellin on the electrocardiogram taken after exertion before and after the drug.

Electrocardiographic tracings were also taken on dogs weighing about 12 kilograms in order to investigate whether massive doses of the drug produce electrocardiographic change. Two hundred fifty mg. injected intramuscularly or intravenously produced no electrocardiographic changes.

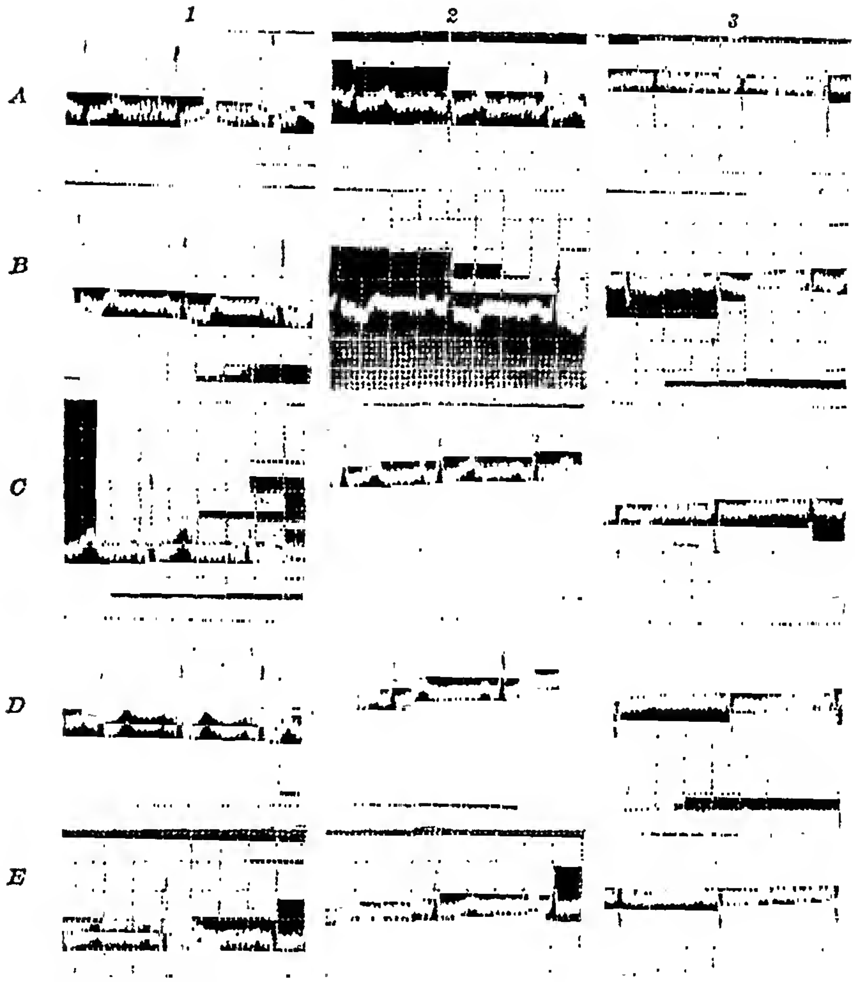


Fig. 4.—*A*, Electrocardiogram before and, *B*, after exertion, showing marked RS-T depression and inversion of T wave.
C, Electrocardiogram before khellin injection.
D, Electrocardiogram immediately after injection of 100 mg. khellin.
E, Electrocardiogram taken after exertion thirty minutes after khellin injection. Note absence of RS-T depression or inversion of T wave.

Side Effects: Some of our patients complained of a sensation of warmth. A few patients complained of mild dyspeptic symptoms after oral administration. Insomnia was also complained of by a few patients. Neither meteorism nor abdominal distension was observed in our series of patients.

The coagulation and bleeding times were estimated in almost all patients and found to be unaffected. The blood pressure, pulse rate, and respiration were unaffected by doses of khellin up to 200 milligrams.

Results in Patients With Coronary Thrombosis.—

Fifty patients with acute coronary thrombosis were subjected to khellin therapy. Twelve patients died during the first or second week of the treatment and thirty-eight patients recovered. In some of these patients the illness was a serious one from the start, but patients with equally serious involvement recovered after khellin treatment. It is very difficult to attribute any improvement to

one or another cause and therefore it is too early to reach definite conclusions. Comparing one group of fifty patients with coronary thrombosis who received khellin with another group of fifty patients who received other coronary vasodilator drugs, there was not much difference in the mortality rate. In the control group, fourteen patients died.

Khellin, together with morphia, was given safely in single doses of 100 mg. and continued in this dosage daily for a period varying from six weeks to three months. The drug controlled and relieved the anginal attacks which followed coronary thrombosis during the period of rest in bed as well as after recovery in twenty-one patients who happened to suffer from such attacks.

The main object of administering khellin to patients with coronary thrombosis was to provide the heart with a coronary vasodilator agent which does not lower the blood pressure or affect the heart muscle. It was also hoped by this therapy to relieve any associated coronary spasm and improve the collateral circulation, and in this way to diminish the area of the cardiac infarct.

Three patients with coronary thrombosis also suffered from auricular fibrillation; all three patients tolerated the drug fairly well and made a good recovery. The drug also appeared to relieve attacks of cardiac asthma occurring in two patients of our series.

COMMENT

Experimental as well as clinical observations show that Ammi Visnaga and its active principle, khellin, can be used as a coronary dilator in the treatment of deficient coronary circulation. As a result of its administration in a series of patients, the number of anginal attacks became less and the cardiovascular tolerance increased. No habituation to the drug seemed to occur. Even after the drug was used for two years, it was still effective. No toxic effects were encountered during its trial for such periods. The drug seems to be safe to administer as well as of value in relieving the coronary spasm occurring during coronary thrombosis. Administered during attacks of angina, it causes relief.

Khellin possesses definite advantages over other known coronary vasodilators. Compared with aminophyllin, for example, the action of khellin is more prolonged; dose for dose, khellin is more potent than aminophyllin. Experimental evidence has shown that the effect of khellin on the coronary blood vessels is about four times stronger than that of aminophyllin. Aminophyllin stimulates the myocardium to increased vigor of contraction. This is accompanied by increased cardiac output and increased work of the heart. Some authors suggest that the increase of the coronary blood flow produced by theophyllin in the experimental animal follows rather than precedes the myocardial stimulation. Khellin does not lower the blood pressure in man, while aminophyllin may affect the blood pressure; this varies according to its method of administration. Khellin does not affect the blood coagulability as aminophyllin is said to do.

SUMMARY

The experimental observations show that khellin is a potent coronary vasodilator; the minimal active concentration of the drug is 10^{-6}. Khellin has a very prolonged action and remains in the circulation for many hours. Its action in dilating the coronary arteries was compared with the similar action of aminophyllin; khellin was found to be at least four times stronger than aminophyllin.

Khellin can be used continuously in the treatment of angina pectoris and also for the relief of individual attacks of pain. It can be administered orally in doses of 50 to 100 mg. three times per day, or as an intramuscular injection in doses of 100 to 200 milligrams. The drug produces a few side effects but is not toxic even after prolonged administration. It does not affect the bleeding or coagulation time.

Altogether 250 patients with angina pectoris were treated with khellin with distinct improvement in 140 cases, with moderate improvement in eighty-five cases, and with no effect in twenty-five cases. In many patients clinical improvement was confirmed electrocardiographically. The drug was used also in fifty patients with recent coronary thrombosis with the object of improving the collateral circulation and relieving any associated anginal symptoms. The latter, at least, seemed to have been accomplished.

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FURTHER STUDIES OF THE CIRCULATION WITH RADIOACTIVE ERYTHROCYTES

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NEW possibilities of investigating the normal and pathological physiology of the human circulation have been opened by De Hevesy's method of labelling human erythrocytes with radioactive phosphate. We have used this method since 1942 to elucidate certain physiological and pathological problems, and have published several papers dealing with these problems. The circulating corpuscular volume has been determined with red cells labelled with radioactive phosphate.

General Method.—In general, the following method has been used: About 8.0 c.c. of blood, taken from an arm vein of the patient, is put into a paraffinized glass flask containing a small amount of heparin to prevent blood clotting, together with a minimal amount of radioactive sodium phosphate. The labelling activity is about 0.05 millicurie. The glass flask is shaken in a special water bath at 37°C. for two hours. By that time the blood corpuscles and the plasma are about equally labelled. About one-half of the 8.0 c.c. of labelled blood is reinjected into the patient and thereafter blood samples are drawn at fixed times after the injection. The activity of the injected samples, and also of the drawn samples, is then measured with a Geiger counter. The plasma and cells are treated separately in each sample. The activity has been expressed as "specific activity," that is, the impulses per gram of plasma or corpuscles per minute. In each experiment about 0.05 millicurie of activity has been injected into the patient. In general, in order to measure the circulatory corpuscular volume and changes in the circulation according to the mixing conditions, we have injected both labelled corpuscles and plasma, that is, the whole labelled blood. In nearly all of our publications we have paid especial attention to the mixing phenomenon in the human body and made rather comprehensive investigations on this extremely interesting question. The earliest part of the mixing curve (or dilution curve) has been achieved by collecting blood samples successively without interruption from the arterial blood practically immediately after the labelled blood has been injected intravenously into the patient.

In our routine determinations of the circulatory blood corpuscular volume we have not taken arterial but venous blood samples and measured the activity

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Presented before the Third Inter-American Cardiological Congress, Chicago, Ill., June 13-17, 1948.

of both corpuscles and plasma in them. With this technique we obtain the results of the specific activity of both plasma and corpuscles according to Fig. 1. We have found rather constantly, as is seen in Fig. 1, that the activity of the plasma decreases very rapidly from the sixth minute after the injection, with the result that there are minimal quantities left in the plasma one to twenty-five hours after the injection. On the other hand, the activity of the red cells remains practically constant up to one hour after the injection and then loses its activity rather slowly, so that six hours after the injection about 10 per cent is lost. The fact that the red cells retain their activity at a rather constant level for at least one hour after the injection makes this method a very suitable one for studying circulatory pnenomena. As a result of this it has been possible to study the changes in the circulatory corpuscular volume in cardiac decompensation (Hedlund) and the influence of the so-called depôt function following muscular exercise and the injection of adrenalin (Nylin). It has also been possible to measure the blood volume of one lung during pulmonectomy, of the lower part of the legs, and the change in the circulatory corpuscular volume after ligation of a patent

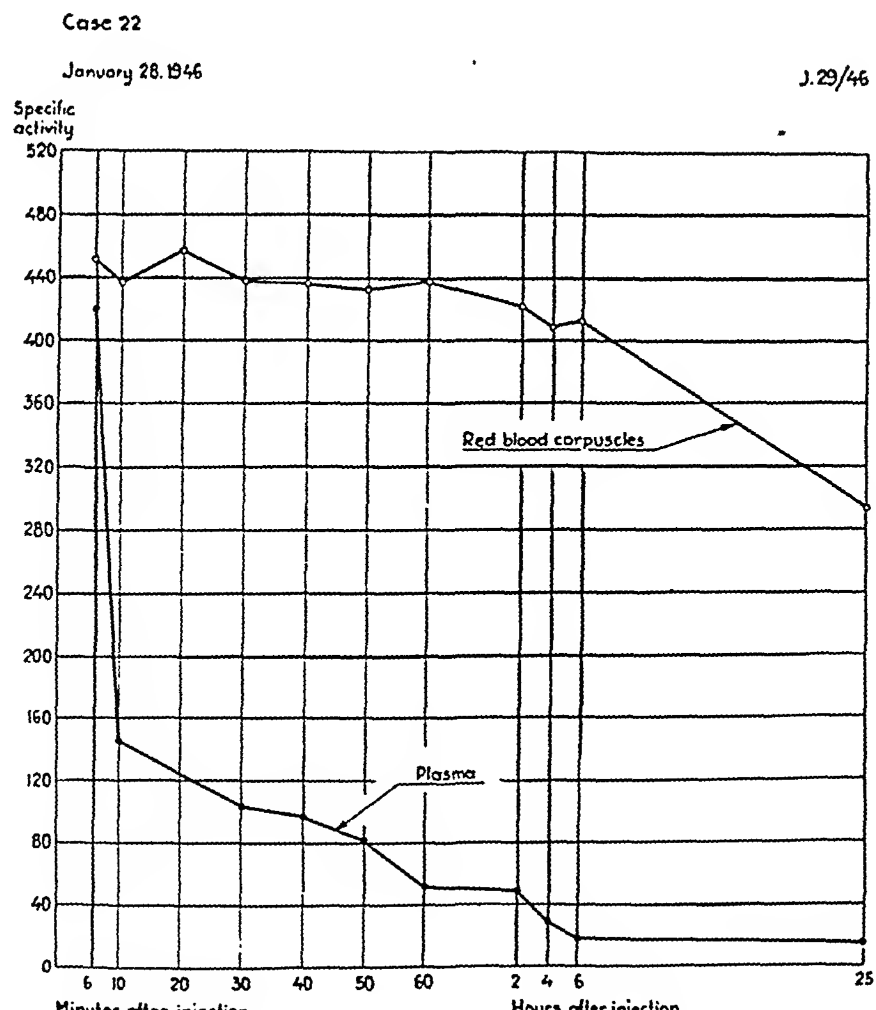

Fig. 1.—Specific activity of red blood corpuscles and plasma during twenty-four hours after intravenous injection of tagged erythrocytes and plasma.

ductus arteriosus. Furthermore, it has been of especial interest to study the mixing conditions of the residual blood of the heart both under physiologic conditions and also in those clinical conditions in which the heart is dilated. The influence of posture on the changes in the residual blood of the heart has been investigated as well. In addition, the changes in the type of the dilution curve in clinical conditions, such as hypotension and shock influenced by spinal anesthesia, have been gone into.

Duration of Specific Activity of Red Cells.—It has been asked if the red cells really retain their constant specific activity after injection for as long as one hour. In order to elucidate this point we have attacked the problem further by means of the following different experiments:

1. We have injected only the red cells. These, after having been separated from the active plasma, were washed twice with the patient's own plasma obtained prior to labelling.

2. We have injected only labelled plasma.

3. We have made double injections of labelled whole blood.

Fig. 2 shows the results of the first method. The diagrams show the change in the specific activity five to sixty minutes and then two, three, twenty, and twenty-four hours after the injection of only labelled red cells. It is remarkable that there is only a small amount of activity of the plasma from the fifth minute up to three hours after the injection of the labelled corpuscles. We suppose that the small quantity of activity of the plasma is due to the fact that we are not able to free the red cells from adherent active plasma even if they are washed twice with unlabelled plasma. The red cells have a constant activity up to

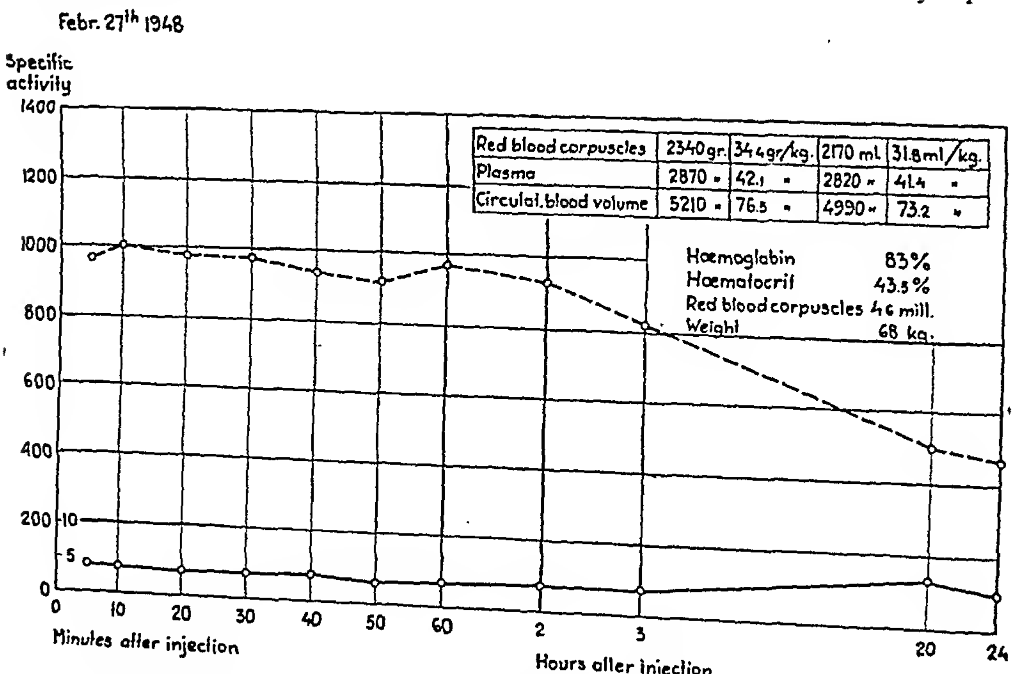

Fig. 2.—Specific activity of red blood corpuscles and plasma after injection of labelled blood corpuscles.

sixty minutes after the injection or even up to two hours after the injection, but they then rather slowly lose their activity. At the same time the slight activity of the plasma probably increases a little twenty to twenty-four hours after the injection of the active red cells.

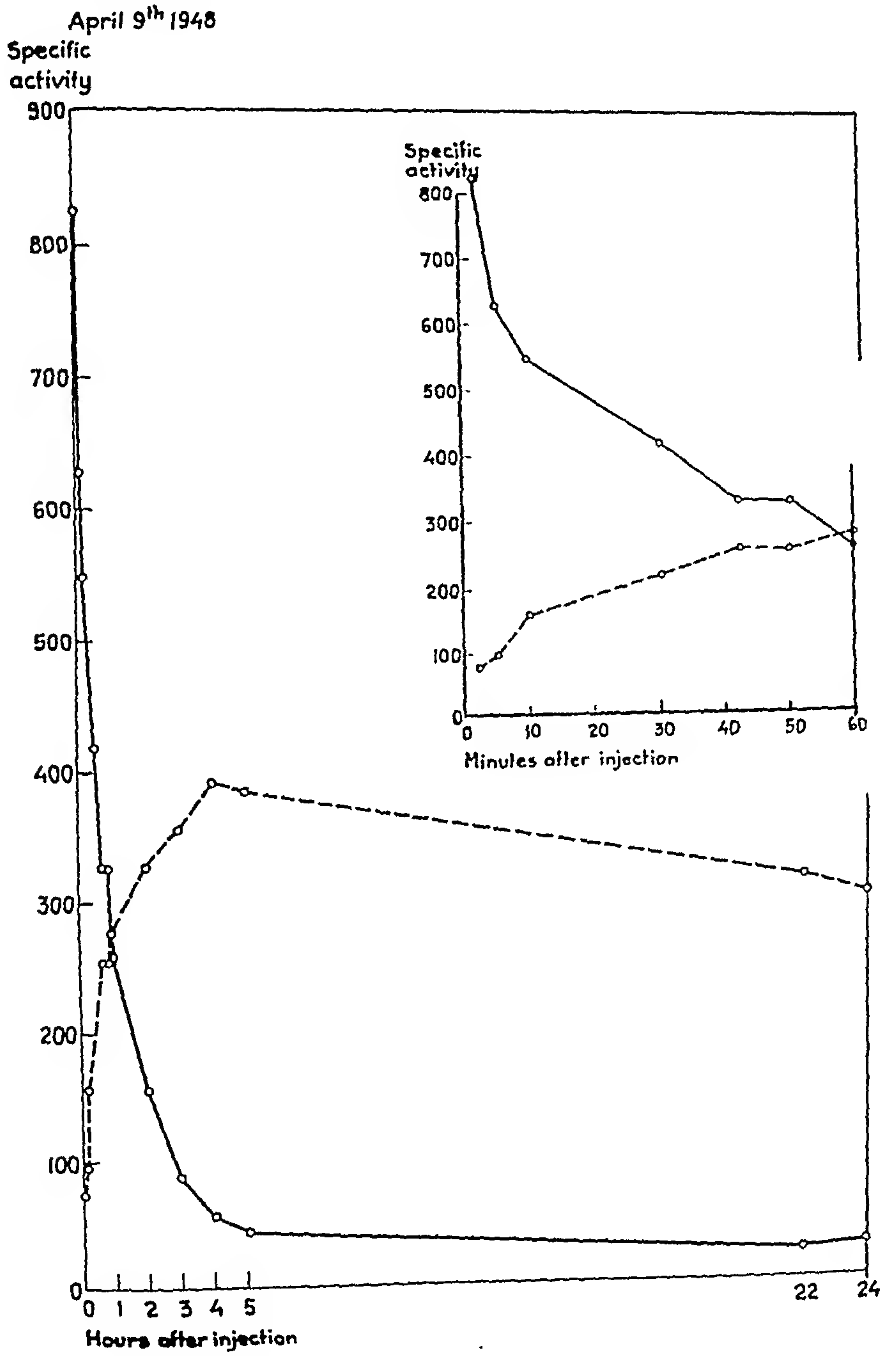

Fig. 3.—Specific activity of red blood corpuscles and plasma after intravenous injection of labelled plasma.

The second experiment of injecting only labelled plasma is instructive. From Fig. 3 one can see that even under these conditions the plasma activity decreases very rapidly up to three, four, or five hours after the injection and

that there still remains a minimal activity twenty-two and twenty-four hours after the injection. On the other hand, the red cells increase their activity for one to five hours after the injection of labelled plasma because radioactive phosphate enters the corpuscles. There is, as has been shown in the figure, probably a maximum labelling of the red cells about five hours after the injection; thereafter, up to twenty-two to twenty-four hours, a rather slow decrease of the activity of the red cells occurs. In the upper right hand corner of Fig. 3 the first part of the curve is enlarged to show the early changes in activity of the labelled red cells and the plasma more clearly. It is rather remarkable that the crossing point of these curves in two experiments in normal persons occurs about sixty minutes after the injection.

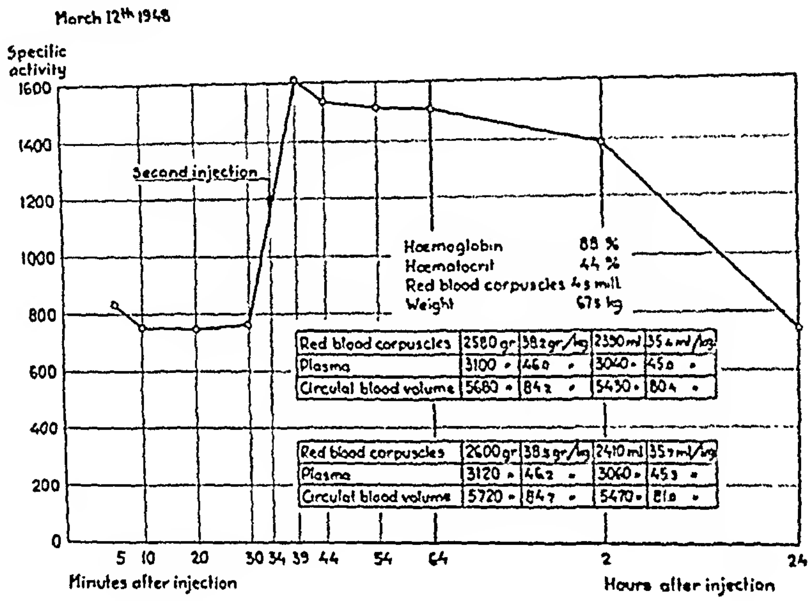

Fig. 4.—Specific activity of red blood corpuscles and plasma after double intravenous injections of labelled whole blood.

The results of the third experiment, in which double injections of labelled whole blood are made, is shown in Fig. 4. The second injection was made thirty-four minutes after the first one. The first part of the curve illustrates the specific activity of the red cells five to thirty minutes after the injection of labelled whole blood and shows that the activity is constant. After the second injection, made thirty-four minutes after the first one, the activity of the red cells is practically constant up to the sixty-fourth minute and then decreases, as has been shown before, rather slowly in twenty-four hours. In this way the second injection may be a control of the determination of the circulatory corpuscular volume, and the agreement between the two determinations in this example is very good. The difference in the weight of the red cells is only 20 grams.

*Determination of Residual Blood of Heart, Minute Volume, and Thoracic Pool of Blood.**—During the last three or four years we have tried to obtain an

*A full description of the method used will be published in the AMERICAN HEART JOURNAL.[19]

idea of the amount of the residual blood in the heart, the cardiac output, and the thoracic pool of blood. We have attempted to obtain these data mathematically from estimations of the dilution curve from the arterial blood.

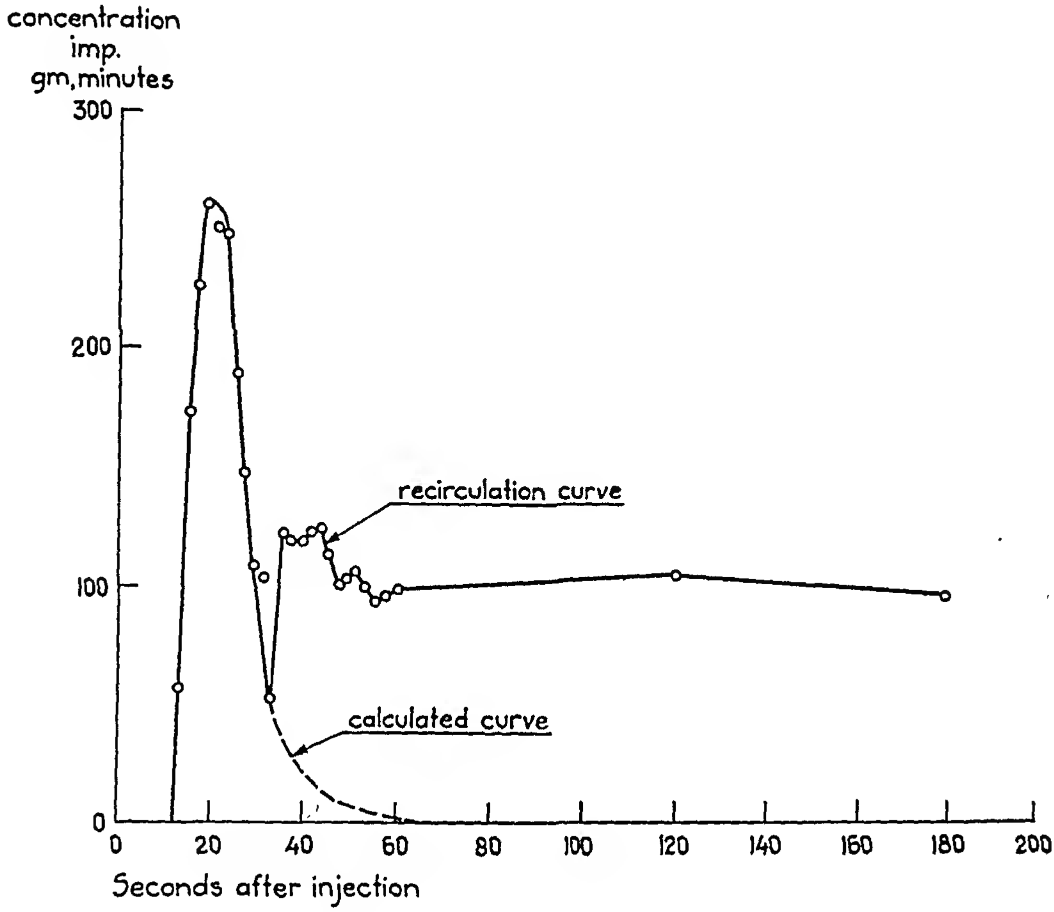

Fig. 5.—Dilution curve. Normal case.

Fig. 5 shows a typical dilution curve of a normal case. After the sample taken at the thirty-fifth minute, where the minimum of specific activity occurs, the calculated curve is dotted. From that point, however, the recirculation curve begins. From a curve of this type, as is shown in Fig. 5 and more schematically in Fig. 6, the cardiac output may be calculated by the aid of the following formula:

$$x = \frac{v_1 \,.\, h_1 \,.\, c_1'}{h \,.\, \int_0^\infty c \,.\, dt}$$

where $x =$ the cardiac output

$v_1 =$ volume of the injected labelled blood

$c_1' =$ concentration of indicator of the injected sample

$h_1 =$ hematocrit of the injected blood

$h =$ hematocrit of the circulating blood

$\int_0^{\infty} c\,dt =$ the area limited by the curve *DAGBJ* (Fig. 6) and the X axis. Of this area, the part *DAGII* must be determined graphically. The part below *GBJ* is determined by the formula:

$$\int_{t_H}^{\infty} c_0 \cdot e^{-\lambda t}\,dt$$

where c_0 and λ are constants which must be determined from the curve segment *GB*.

$e =$ the base of the natural log system.

All the time units are in minutes. All volumes in liters.
An upper limit for the pool volume is $x \cdot \Delta t$
A lower limit for the pool volume is $\frac{x}{\lambda}$

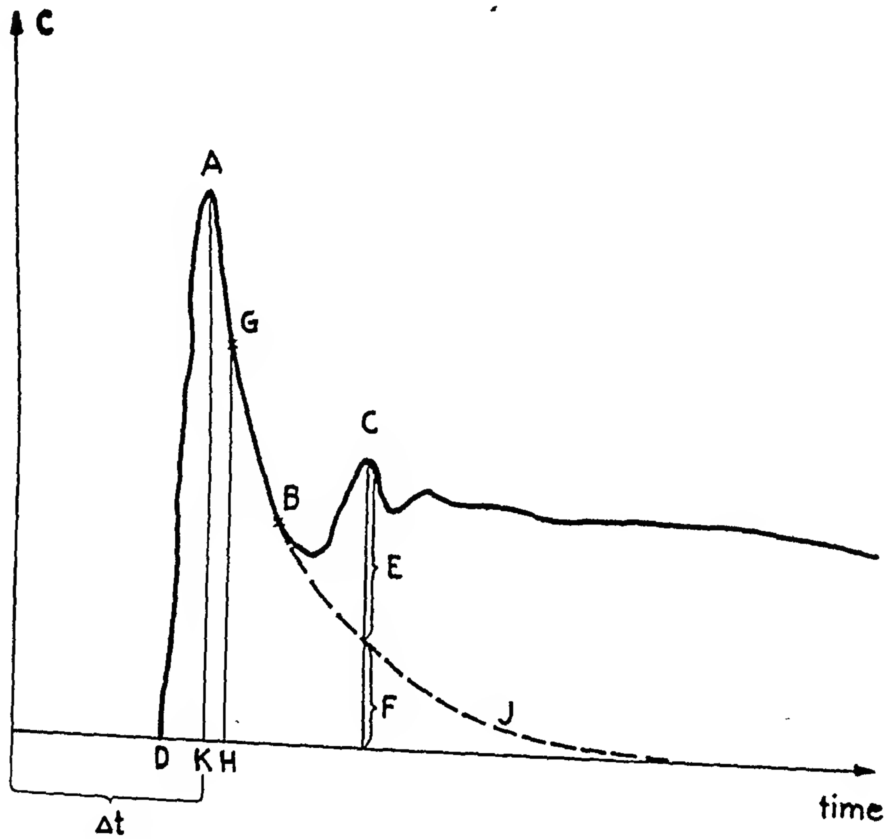

Fig. 6.—A dilution curve schematically represented. Discussed in text.

CONCLUSIONS

Detailed studies concerning the level of the corpuscular and plasma activity after (a) injection of labelled cells only, (b) injection of labelled plasma only, and (c) double injections of labelled whole blood show the following:

1. Injected labelled red cells remain constant in their activity for at least one hour after injection. The activity of labelled plasma, when given by itself, decreases very rapidly. On the other hand, the radioactive phosphate from the plasma enters very slowly into the corpuscles and reaches a maximum in the corpuscles about five hours after injection. It seems to be a normal finding that the activity of the red cells and also of the plasma is the same about sixty minutes after injection.

2. Double injections of whole blood, the second injection being given about thirty minutes after the first injection, give the same calculated blood corpuscular volume as determined from the first injection. This can be used as a control.

3. With the help of the injected labelled corpuscles it is possible to calculate the minute volume of the heart and the thoracic pool of blood from the dilution curve in the arterial blood.

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COMPLETE TRANSPOSITION OF THE AORTA AND A LEVOPOSITION OF THE PULMONARY ARTERY

Clinical, Physiological, and Pathological Findings

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THE clinical findings presented in the following case report represent a syndrome which we have seen not infrequently in recent years in the cardiac clinic of the Harriet Lane Home. This is, however, the first instance in which it has been possible to correlate the clinical findings with the autopsy findings. The case clarified the nature of the malformation and unfortunately demonstrated one of the most serious dangers of angiocardiography. Hence, the case is reported in detail.

CASE REPORT

P. A. W. (H. L. H. A-60186), a 5½-year-old white girl, was referred to the clinic for diagnosis of her cardiac abnormality.

The family history was noncontributory. The mother had not had German measles nor any rash or unexplained fever during her pregnancy. There was no familial history of congenital abnormalities.

The past history indicated that cyanosis was noted at birth and persisted throughout her life. At 3 weeks of age, a murmur was heard over the precordium. During infancy she gained weight slowly. At the age of 1 year she weighed 7.6 kilograms. Her development was also slow: she sat alone at 9 months and walked at 2 years. When about 3 years of age she frequently squatted down to rest, but soon outgrew the habit.

Physical Examination.—The temperature was 37° C., pulse 120, respiration 30, height 110 cm., weight 15.6 kilograms, and blood pressure 100/80. The child was an intelligent, moderately cyanotic, poorly developed girl who suffered from dyspnea at rest. There was suffusion of the conjunctivae. The lips and buccal mucous membranes were deeply cyanotic. The tonsils were small. The teeth were in good condition. The heart was slightly enlarged. The rhythm was regular. A systolic murmur was audible over the precordium which was definite but not loud; no thrill could be felt. The lungs were clear to percussion and auscultation. The liver and spleen were not palpable. The pulse in the femoral artery was of good quality. There was cyanosis and clubbing of the fingers and toes.

Laboratory Data.—The red blood cell count was 9.3 million. Hemoglobin concentration was 23.5 grams. The hematocrit was 77. Arterial blood analysis showed an oxygen content of 17.4 volumes per cent, oxygen capacity of 30.8 volumes per cent, oxygen saturation of 57 per cent, and carbon dioxide content of 25.8 volumes per cent.

From the Departments of Pediatrics and Surgery of the Johns Hopkins Hospital and from the Cardiac Clinic of the Harriet Lane Home, Johns Hopkins Hospital, Baltimore, Md.
Presented before the Third Inter-American Cardiological Congress, Chicago, Ill., June 13-17, 1948.

Teleroentgenogram.—The heart was slightly enlarged. There was fullness of the pulmonary conus and the hilar markings were increased (See Fig. 1).

Fluoroscopy.—The findings in the x-ray film were confirmed and, in addition, fluoroscopy revealed faint expansile pulsations of the hilar shadows. Delineation of the esophagus with a barium-opaque mixture showed a left aortic arch and no evidence of left auricular enlargement.

Electrocardiogram.—There was a normal sinus mechanism, sinus tachycardia, normal P-R interval, high P waves in the second lead, right axis deviation, and right ventricular hypertrophy.

Clinical Impression.—The clinical findings were characteristic of an Eisenmenger complex in that there was cyanosis, clubbing, and polycythemia; the heart was slightly enlarged with x-ray evidence of fullness of the pulmonary conus and increased hilar shadows, which upon fluoroscopy showed faint expansile pulsations. However, the fact that cyanosis dated from birth made us suspect some totally different malformation.

Fig. 1.—Teleroentgenogram of the chest, anterior-posterior position.

In Norway in the summer of 1947, one of us (H. B. T.) had been told of an infant with a similar clinical history. In this instance, examination of the heart showed an unusual anomaly of the great vessels: the aorta, which was abnormally small, arose from the right ventricle and the pulmonary artery was greatly enlarged and overrode the ventricular septum. For this reason, in the case under discussion, an overriding pulmonary artery was postulated, but, because of the

age of the patient and child's comparative well-being, the transposition of the aorta was not suspected.

Inasmuch as the diagnosis in this instance was obscure, the patient was referred to the physiological laboratory for special studies by one of us (R. J. B.) and to the x-ray department for angiocardiography.

Results of Physiological Studies.—Results obtained from the standard exercise test[1] showed that the oxygen consumed per liter of ventilation fell from 17 to 12 cubic centimeters. From this, it was inferred that the effective pulmonary blood flow through the lungs did not increase normally with exercise.

The results of cardiac catheterization are given in Fig. 2. It may be seen that the oxygen content of the right ventricular blood was significantly higher than that of the right auricle, indicating the presence of a ventricular septal defect. Of special interest was the finding that the oxygen content of the pulmonary arterial blood exceeded that of the right ventricular blood by 4.4 volumes per cent. The finding suggested admixture of oxygenated blood with right ventricular blood. A gradient of this magnitude between the right ventricular blood and the pulmonary arterial blood could have been the result of a ductus arteriosus, or of a communication between the pulmonary artery and the left ventricle through a high ventricular septal defect with the pulmonary orifice overriding the lower portion of the ventricular septum. The clinical findings, however, rendered unlikely the diagnosis of a patent ductus arteriosus as there was no continuous machinery-like murmur. Furthermore, the peripheral arterial oxygen saturation was only 57 per cent. It seemed almost certain that a large patent ductus arteriosus would increase the effective pulmonary blood flow sufficiently to raise the oxygen saturation of peripheral arterial blood to a higher level. It was, therefore, assumed that the pulmonary artery received oxygenated blood directly from the left ventricle.

Fig. 2 shows that the oxygen content of peripheral arterial blood was 7.6 volumes per cent less than that of the pulmonary arterial blood and 3.2 volumes per cent less than that of the right

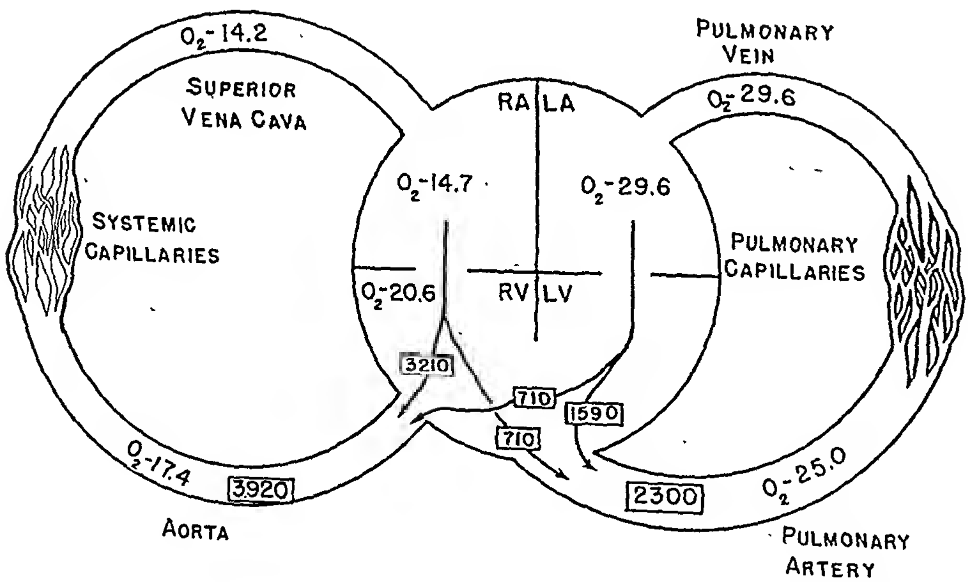

Fig. 2.—Diagram illustrating intracardiac hemodynamics. O_2 indicates oxygen content of the blood in volumes per cent. Oxygen content of the blood in pulmonary vein was calculated on the assumption that the blood was 96 per cent saturated.[2] Figures in boxes give volume of blood flow in cubic centimeters per minute per square meter of body surface. It may be seen that the large volume of the right auricular blood flows directly from the right ventricle into the aorta and only a small volume of blood passes into the pulmonary artery. This latter represents the effective pulmonary blood flow.

ventricular blood. This finding indicated that the aorta must receive a large quantity of unoxygenated blood. This could be the result of a high septal defect with the aorta overriding the ventricular septum or a complete transposition of that vessel. Although the latter possibility seemed likely, the physiological data alone were insufficient to establish the diagnosis. The pressures recorded in the pulmonary artery were 57/45 mm. of mercury; those in the right ventricle were 42/19 mm. of mercury (Fig. 3).

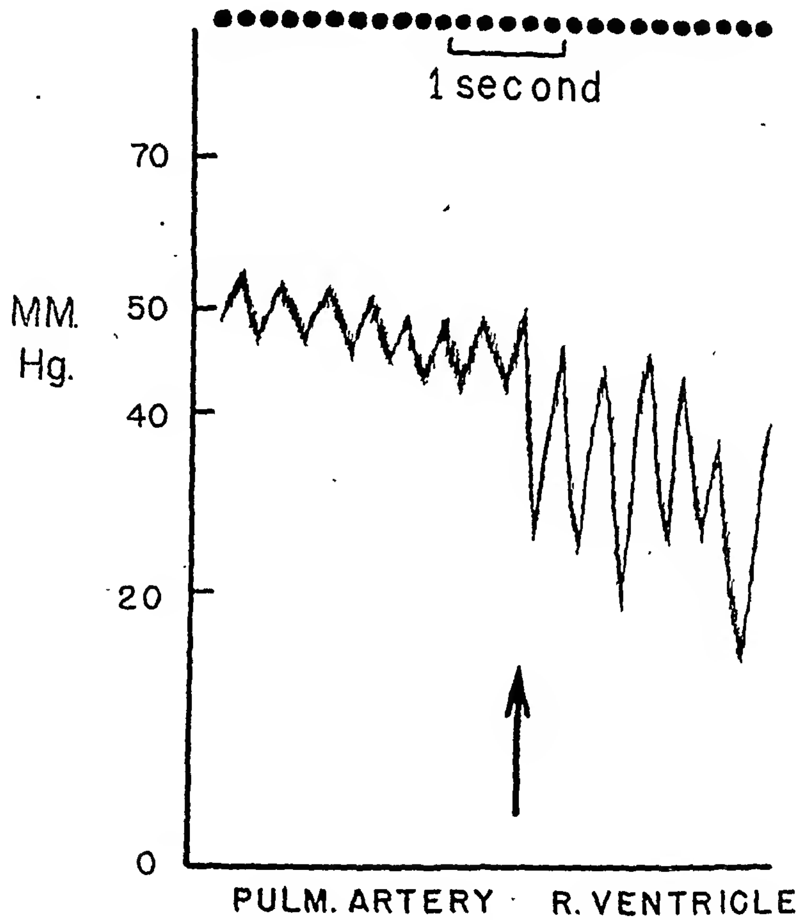

Fig. 3.—Continuous tracing of direct strain-gauge recording obtained in the pulmonary artery and in the right ventricle. The arrow indicates the point at which the tip of the catheter passes through the pulmonic valve into the right ventricle.

Angiocardiography.—After an initial test dose, the patient was given 19 c.c. of 70 per cent Diodrast intravenously through a canula and a series of eight films were taken in eight seconds. Thirty minutes later she was given another dose of 19 c.c. and a second series of eight films were taken. Because of a mechanical defect, no exposures were obtained. Therefore, fifteen minutes later, a third dose of 19 c.c. of Diodrast was injected and a series of eight films were photographed in eight seconds. There was no immediate reaction, but three minutes thereafter the child sat bolt upright and the heart stopped. All effort at resuscitation failed.

The angiocardiograms showed that the dye entered the right auricle and then the right ventricle; immediately thereafter the aorta was promptly visualized. Very little dye was seen in the pulmonary artery or the lungs. The circulation of the dye could not be traced further. The second series of films taken in the lateral position showed that the aorta appeared to arise from the anterior portion of the right ventricle. Again, the circulation of the dye could not be traced into the lungs, nor to the left side of the heart.

Final Clinical Diagnosis.—The physiological studies and angiocardiograms indicated a transposition of the great vessels. The x-ray and fluoroscopic findings indicated that such was not the case in that the pulmonary artery appeared to arise from the right ventricle.

Autopsy (No. 21039, Performed by Dr. Edmund Novak).—The chief interest centered about the heart. It weighed 180 grams. The right auricle was not greatly enlarged. The superior vena cava and the inferior vena cava opened into it in the normal fashion. The foramen ovale was completely covered by a valve, but there was probe patency of the valve for a distance of 1.0 cm. along its margin. The tricuspid valve, which was slightly thickened, opened into the right ventricle. That chamber was tremendously hypertrophied; its wall measured 1.5 cm. in thickness. The pulmonary artery arose approximately in its normal position. The aorta was transposed; it arose entirely from the right ventricle. The aortic orifice lay adjacent to the pulmonary orifice and to the ventricular septum as shown in Figs. 4 and 5. The aortic valve had three cusps and the coronary arteries were given off from the aorta in the normal manner. The aortic ring meas-

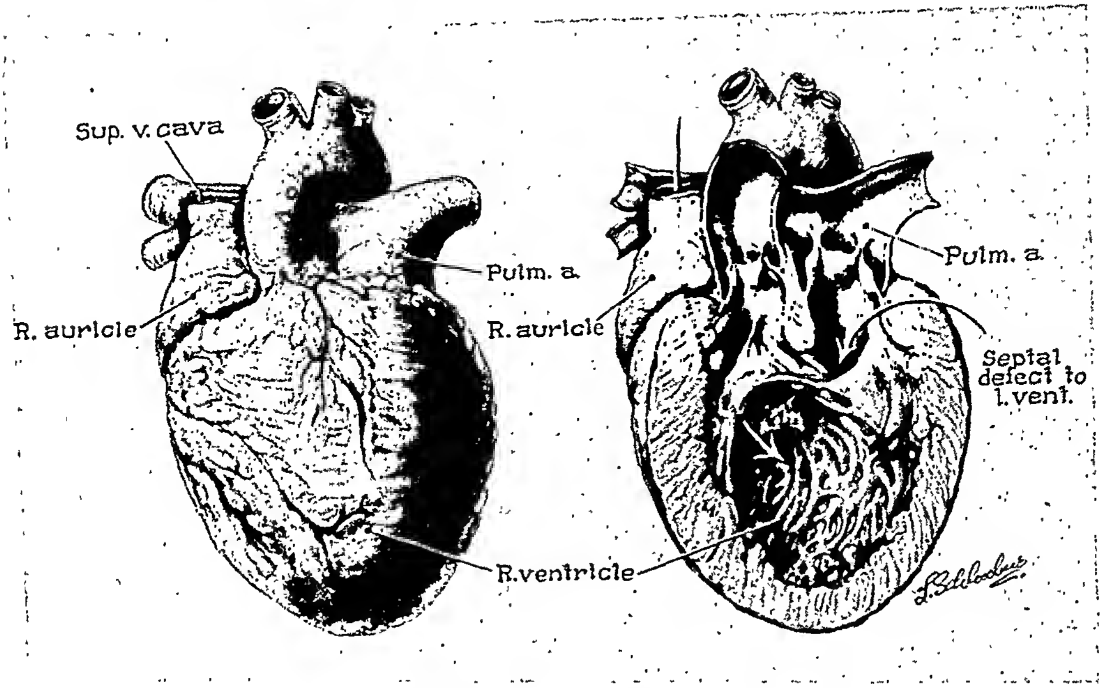

Fig. 4.—Drawing of the heart showing size and position of the aorta and pulmonary artery and their relation to the septal defect.

ured 3.5 cm. in circumference. The aorta and its branches appeared to be normal. The maximum circumference of the ascending aorta was 4.0 centimeters. At the base of the ventricular septum, the septal wall was defective for a distance of 1.2 cm. and the defect extended downward toward the apex for approximately 0.6 centimeter. The superior portion of the ventricular septum deviated to the right to such an extent that the pulmonary orifice overrode the septal defect by a few millimeters. From the upper margin of the ventricular septum close to the defect, a muscular ridge extended forward to the outer wall of the right ventricle. This ridge separated the aorta from the pulmonary artery. Consequently, the aorta arose entirely from the right ventricle and only the pulmonary orifice overlay the ventricular septum. Thus, the pulmonary artery not only received blood from the right ventricle, but also received blood directly from the left ventricle. The pulmonary artery and its branches were greatly dilated. The pulmonary orifice measured 5.8 cm. in circumference and the main pulmonary artery above the ring had a circumference of 6.5 centimeters. The left main branch measured 4.0 cm. in circumference; the right

branch was approximately the same size. The pulmonary arterial wall was thicker than normal; its intima, however, was smooth. The ductus arteriosus was closed. The examination of the myocardium showed that the fibers were hypertrophied but there were no infarcts and no thrombi. The coronary arteries appeared to be normal. The bronchial arteries were not enlarged.

The lungs were air containing and showed no evidence of pneumonia or pulmonary infarcts; all the pulmonary vessels were patent. Microscopic examination of the lungs revealed occasional thrombi, some of which were in the process of recanalization. Many of the small pulmonary arterioles showed diffuse, intimal proliferation which rendered these vessels extremely narrow. The lesion appeared to be sufficient to account for the increased resistance in the pulmonary vascular bed. In addition, the pulmonary alveoli showed areas of emphysema and areas of atelectasis.

The liver showed marked congestion. The spleen was enlarged and showed evidence of congestion; it weighed 140 grams. There were many small accessory spleens. The kidneys were normal except for congestion; each weighed 80 grams. The cortex and medulla were well defined. The pelvis and ureters were not remarkable. There was a diffuse hemorrhage in the thymus.

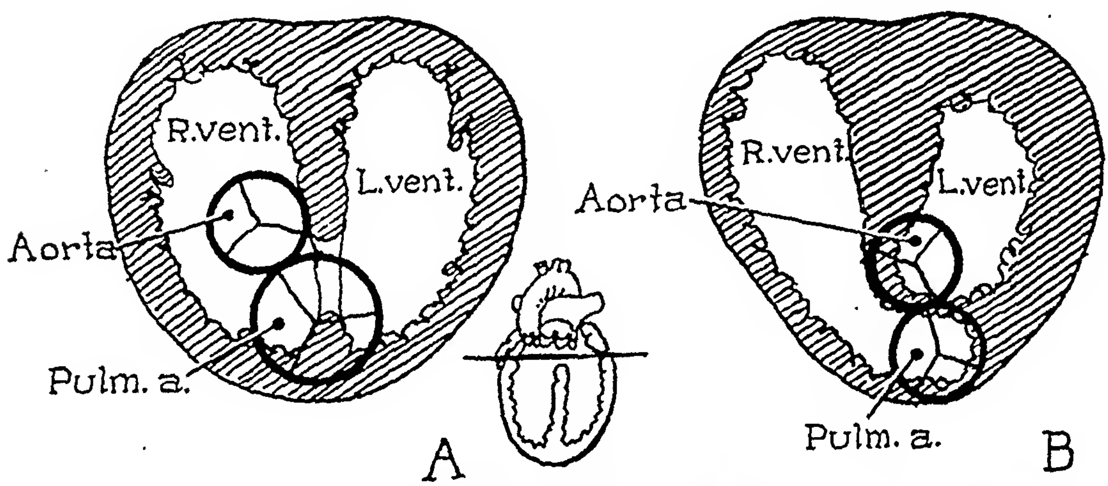

Fig. 5.—Cross section of the heart illustrating the relation of the aorta and the pulmonary artery to the ventricular septum, *A*, in this malformation and *B*, in the normal heart.

Final Anatomical Diagnosis.—Transposition of the aorta. Dilatation and slight displacement of the pulmonary artery. Ventricular septal defect. Foramen ovale covered by a valve, but not completely sealed. Dilatation and hypertrophy of the right ventricle. Extreme thickening and intimal proliferation of the pulmonary arterioles and small arteries. Occasional recanalization of thrombi in the pulmonary arterioles. Splenomegaly. Patchy emphysema and atelectasis. Acute congestion of the lungs and viscera. Diffuse hemorrhage in the thymus.

DISCUSSION

Autopsy showed that the aorta was transposed and the pulmonary artery arose primarily from the right ventricle, but overrode the ventricular septum and received blood directly from both ventricles. This malformation is tabulated by Pernkopf[3] as one of the possible combinations which may occur in transpositions of the great vessels.

The malformation was similar to the one the author had seen in Norway, except that the aorta was not abnormally small and the ventricular septal defect was larger than in the Norway specimen. These two factors rendered the malformation more readily compatible with life.

This malformation produces a syndrome which is clinically similar to that associated with an Eisenmenger complex. In both conditions the pulmonary artery arises from the right ventricle; in both, the contour of the heart in the x-ray film shows fullness of the pulmonary conus. Both have large pulmonary arteries, which upon fluoroscopy usually show expansile pulsations. In both malformations the heart is but slightly, if at all, enlarged; both have a systolic murmur; both show evidence of right axis deviation and right ventricular hypertrophy. Both conditions are compatible with life for a number of years. In both, the habit of squatting is either entirely absent or of short duration. The outstanding clinical difference between this malformation and the Eisenmenger complex is that in the former, cyanosis dates from birth, whereas the late development of cyanosis, at or about the time of puberty, is characteristic of the Eisenmenger complex. Both conditions lead to polycythemia and clubbing of the extremities which, however, occur at a later date in patients with an Eisenmenger complex than with this malformation.

Anatomically, this malformation differs from an Eisenmenger complex in that the aorta is not dextroposed; that is, it does not arise from the left ventricle and partially override the ventricular septum, but it is *transposed* and arises entirely from the right ventricle. Furthermore, it is the pulmonary artery, not the aorta, which overrides the ventricular septum.

The origin of the aorta from the right ventricle means that the blood from the right ventricle is pumped directly into the aorta; this readily explains the early appearance of cyanosis. Indeed, the only oxygenated blood to reach the aorta is that which is shunted from the left ventricle through the septal defect into the right ventricle. Inasmuch as the pulmonary artery overrides the ventricular septum, blood from the left ventricle is readily directed into the pulmonary artery.

Functionally, this malformation closely resembles the malformation in which both the aorta and the pulmonary artery arise entirely from the right ventricle and the septal defect lies beneath the pulmonary artery. This last mentioned malformation is also mentioned by Pernkopf[3] and has been classified by some as an Eisenmenger complex, but is totally different from the malformation originally described by Eisenmenger and, to use Dr. Maude Abbott's words, "is not to be confused with an Eisenmenger complex." Therefore, the authors feel that the term "Eisenmenger complex" should be limited to the type of malformation originally described by Eisenmenger and that the combination of a transposed aorta with a pulmonary artery which arises from the right ventricle and partially overrides the ventricular septum represents a separate clinical and pathological entity. Furthermore, the malformation, in which both great vessels arise from the right ventricle and in which the septal defect is adjacent to the posterior margin of the pulmonary orifice, is functionally more closely related to the malformation under discussion than to the Eisenmenger complex.

The origin of the aorta from the right ventricle means that venous blood is directed into the aorta and, consequently, the oxygen saturation of the arterial blood is abnormally low. Exercise causes a further fall in the oxygen saturation

of the arterial blood and a fall in the oxygen consumption per liter of ventilation. The latter finding is similar to that which occurs in a patient with a tetralogy of Fallot and, not infrequently, with a complete transposition of the great vessels, but is contrary to that which occurs in a patient with an Eisenmenger complex.

Cardiac catheterization reveals a high pressure in the right ventricle and a markedly higher oxygen content in the right ventricle than in the right auricle (Fig. 2). Therefore, if the pulmonary artery is not catheterized, the findings are similar to those in a tetralogy of Fallot. If the pulmonary artery is catheterized, the pulmonary pressure will be found to be high and the oxygen content in the pulmonary artery will be higher than that in the femoral artery.

The intracardiac hemodynamics of this patient are illustrated in Fig. 2. Her oxygen consumption was 105 c.c. per minute per square meter of body surface. As shown in Fig. 2, the systemic flow was 3,920 c.c. per minute per square meter of body surface and the pulmonary artery flow was 2,300 c.c. per minute per square meter of body surface. Thus, the systemic flow exceeded the pulmonary artery flow by 1,620 cubic centimeters. Both were calculated according to formulas published in a previous communication.[2] The effective pulmonary blood flow is the quantity of blood which, after having been returned to the right auricle from the body, is eventually aerated in the lung.[2] In this patient, it will be represented by the volume of mixed venous blood which enters the pulmonary artery from the right ventricle. Consequently, it can be calculated from the oxygen content of the blood in the right auricle and the oxygen content of the blood returned to the left auricle.[2] In this instance, the effective pulmonary blood flow was found to be 710 cubic centimeters. This means that, although the volume of the pulmonary blood flow is 2,300 c.c., only 710 c.c. are mixed venous blood; the remainder is arterial blood which is recirculated through the lungs. Furthermore, in order to keep the pulmonary flow at its calculated constant value, 710 c.c. must be shunted from the left ventricle into the aorta. Since this represents the oxygenated component of the blood supplied to the systemic circulation, it represents the effective systemic flow. The remaining 3,210 c.c. of the systemic flow is mixed venous blood from the right auricle which passes into the right ventricle and is pumped out into the aorta and recirculated through the body.

The relatively small volume of blood entering the aorta from the left ventricle furnishes the only means by which oxygenated blood reaches the body. This explains the low oxygen saturation in the peripheral arterial blood and the severe cyanosis. Consequently, any diminution of this volume may have dangerous consequences.* This may explain the fatal outcome of angiocardiography.

*It is our belief that any condition in which the injection of Diodrast decreases the supply of oxygen to the individual is extremely dangerous. The danger of angiocardiography in pulmonary arteriovenous aneurysms is well known.[4] Under such circumstances, the dye is laked in the aneurysms and interferes with the exchange of oxygen in the lungs. Angiocardiography also proved fatal in a man with a cor pulmonale in whom the pulmonary arteriolar disease caused difficulty in the circulation of the blood through the lungs and in the oxygenation of the blood in the lungs. Recently, a child with an extreme pulmonary stenosis and no ventricular septal defect died after the injection of a single dose (9 c.c.) of Diodrast. In this instance, the orifice into the pulmonary artery was only 1.0 mm. in diameter and the expulsion of dye through this tiny orifice cut off the entire blood supply to the lungs and thereby deprived the child of its sole supply of oxygenated blood.

In this malformation, the increased pressure in the right side of the heart may have blocked the supply of oxygen to the systemic circulation.

In this instance, the rapid injection of the Diodrast into the superior vena cava raised the pressure in the right side of the heart and, consequently, decreased the left-to-right shunt. For this reason, angiocardiography was exceptionally dangerous for this patient. Furthermore, angiocardiography did not clarify the nature of the malformation and therefore is not necessary to establish the diagnosis.

SUMMARY

A new clinical syndrome is described. The malformation consists of a transposed aorta, a large pulmonary artery which arises primarily from the right ventricle and partially overrides the ventricular septum, a high ventricular septal defect, and right ventricular hypertrophy.

Clinically, in this instance the heart was but slightly, if at all, enlarged; there was a systolic murmur and thrill. Cyanosis dated from birth. Clubbing of the extremities developed at an early age. The red blood cell count, the level of the available hemoglobin, and the hematocrit reading were increased. The electrocardiogram showed evidence of right ventricular hypertrophy. The x-ray films of the heart showed fullness of the pulmonary conus and increased hilar shadows. Upon fluoroscopy, the pulmonary vessels showed faint expansile pulsations. The oxygen saturation of the arterial blood was abnormally low and fell still further with exercise.

In brief, the clinical syndrome associated with this malformation resembled that of an Eisenmenger complex, except that cyanosis dated from birth.

The two conditions showed a further difference in that, in the Eisenmenger complex, exercise causes an increase in the consumption of oxygen per liter of ventilation, whereas in this malformation, exercise causes a decline in the oxygen consumption per liter of ventilation.

Intracardiac catheterization studies revealed a higher oxygen content in the pulmonary artery than in the femoral artery. It is probable that the volume of blood which entered the pulmonary artery from the right ventricle was equal to that directed from the left ventricle into the aorta. The extensive intimal changes in pulmonary arterioles appeared to be sufficient to account for the increased resistence in the pulmonary vascular bed.

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STUDIES ON THE CORONARY CIRCULATION

IV. The Effect of Shock on the Heart and Its Treatment

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SHOCK is a common, dreaded complication of coronary artery occlusion. It has been shown that in coronary artery occlusion, patients who develop shock have a much poorer prognosis than those who do not. Recent studies have also demonstrated the deleterious effects of shock on the myocardium.[1-7] In acute coronary artery occlusion, physicians look upon the development of pallor, weakness, sweating, fast weak pulse, poor heart sounds, and gallop rhythm as ominous signs. Most of our knowledge of shock is a result of the study of traumatic shock. Thus, for example, the mechanism and treatment of shock accompanying burns is infinitely better understood than that with coronary artery occlusion. A large percentage of patients die as a result of shock after coronary artery occlusion, and, except for a few poorly studied procedures, there is no well-defined treatment for this type of shock. Thus, the subject was considered worthy of investigation.

At present, the usual treatment for the patient in shock from coronary artery occlusion is heavy sedation, oxygen, coronary dilator drugs, and watchful waiting. Many[8,9,10] believe that shock after coronary occlusion is a "compensatory" phenomenon which reduces the work of the heart. They therefore believe that it should not be treated. From the evidence of the investigations to be presented, we feel that it is probably just as important to treat the shock which follows coronary artery occlusion as that which follows surgery or trauma.

Previous investigations from this laboratory with the use of radioactive red blood cells, fluorescein, and microsphere perfusion have demonstrated that after coronary occlusion blood enters the ischemic region of myocardium through interarterial anastomoses of arteriolar size.[11,12] These investigations also revealed that the collateral blood supply to the epicardial portion of ischemic myocardium

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Motion pictures of these experiments were presented at the conventions of The American Heart Association, Atlantic City, June 6, 1947, The American College of Physicians, San Francisco, April 23, 1948. The Third Inter-American Cardiological Congress, Chicago, June 13-17, 1948. The American Heart Association, Chicago, June 19, 1948, and The American Medical Association, Chicago, June 21-25, 1948.
Photographic reproductions published in this article were taken from these films. The motion pictures, of course, demonstrate the phenomena more clearly than still photographs.

was much better than that to the endocardial portion and that the collateral circulation of the right ventricle was better than that of the left ventricle. The numerous anastomoses between the normal coronary arteries of a dog have been visually demonstrated by cinematographic studies of the beating dog's heart by the injection of air or colored viscid solution into the ligated anterior descending branch of the left coronary artery 3.0 to 6.0 cm. proximal to the tie, and also by the injection of fluorescein into the cannulated anterior descending artery.[13]

It was the purpose of this study to determine the effect of shock on the heart. Therapeutic procedures are suggested as a result of the extensive data that have been obtained.

PART I. EXPERIMENTAL STUDIES OF THE EFFECT OF SHOCK ON THE CORONARY CIRCULATION OF DOGS

Experiment I. The Effect of Shock on the Collateral Circulation Studied by Means of the Radioactive Red Blood Cell Technique.—

Method: Radioactive erythrocytes are easily prepared by the incubating of red blood cells with phosphorus 32. After repeated centrifugation and washing of the cells, they are a useful tool for studying the coronary circulation. By knowing the amount of radiation a known volume of radioactive red blood cells emits, one can easily and accurately determine the volume of blood per gram of tissue by means of a Geiger counter. Furthermore, the heart of an animal injected with radioactive erythrocytes can be placed against a piece of unexposed x-ray film and a radioautograph can be prepared. A shadow is produced by the beta rays from the phosphorus in the red blood cells and the intensity of the shadow is proportional to the number of red cells at any particular area. Details of this method and the results in dogs with coronary occlusion and normal blood pressure have already been presented.[12]

Nine dogs were anesthetized with intravenous Nembutal. Artificial respiration was maintained by means of a tracheal catheter, and blood pressure was recorded by means of a mercury manometer connected to a cannula in the femoral artery. The chest and pericardium were opened and the anterior descending artery was ligated 1.0 to 3.0 cm. from its origin. The blood pressure was lowered to severe shock levels by hemorrhage from the femoral artery or by ventricular fibrillation, after which the radioactive red blood cells were injected intravenously and in the same quantity and manner as in the previous experiments. The hearts were stopped instantly by a freezing mixture of methyl cellosolve in carbon dioxide snow being poured on them one to four minutes after the injection of radioactive erythrocytes. The hearts were removed and opened by Schlesinger's technique. Determinations of the distribution and concentration of the red blood cells in nonischemic and ischemic myocardium were made by means of Geiger counts and radioautographs.

Results: The concentration of radioactive red blood cells in the ischemic region was markedly reduced on both the endocardial and pericardial surfaces of the hearts of dogs in shock. This is in contradistinction to results obtained in dogs with coronary artery ligation and normal blood pressure. In the hearts of

such dogs the quantity of radioactive red blood cells in the pericardial part of the ischemic myocardium was equal to that in the nonischemic muscle. In Fig. 1, a radioautograph of the pericardial surface of the heart of a dog in shock demonstrates this finding. Even more important is the fact that in the shocked dogs the quantity of radioactive red blood cells in control regions of myocardium was markedly diminished when compared with the quantity of cells in control regions

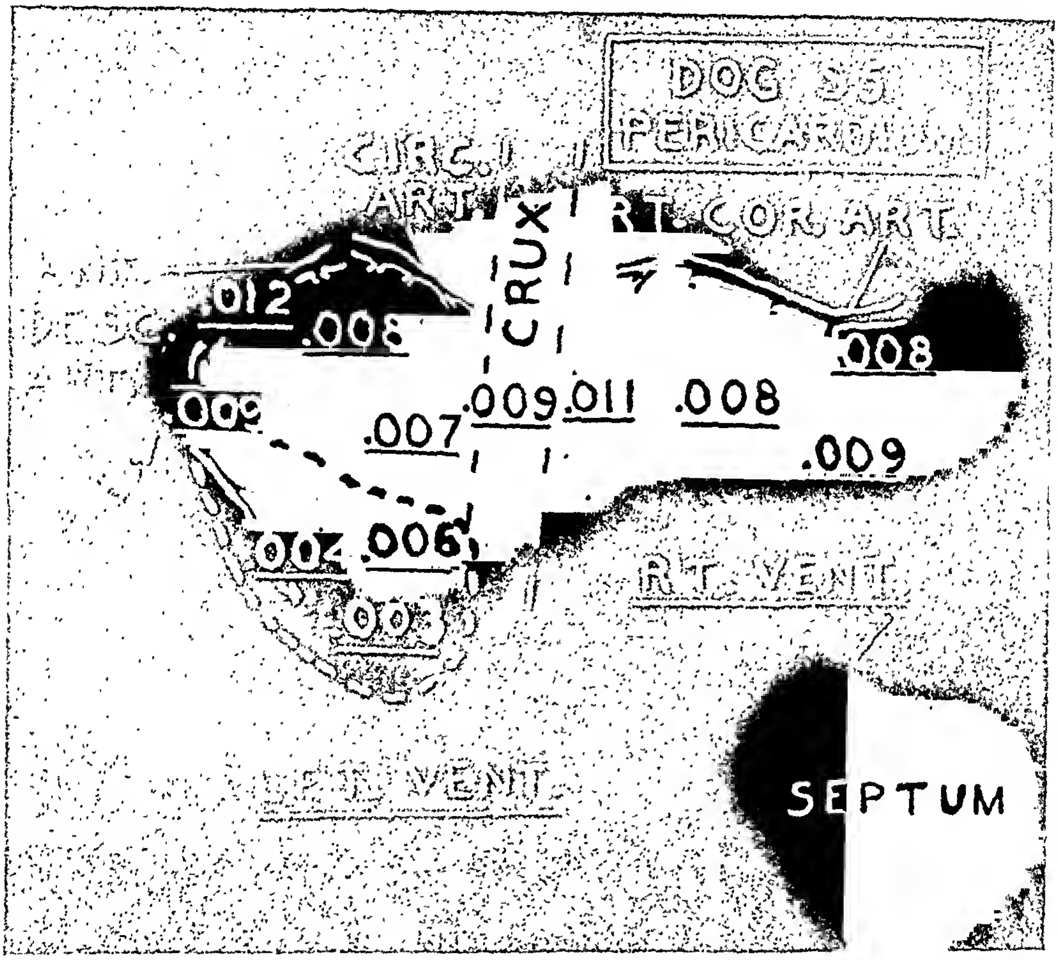

Fig. 1.—Radioautograph of heart of dog in shock with low blood pressure. Anterior descending coronary artery ligated. The figures indicate the volume of blood per gram of tissue as determined by Geiger counts. Note significant reduction in concentration of radioactive red blood cells in ischemic region outlined by dotted line.

of animals with normal blood pressure (Fig. 2). These results indicate that after shock the general coronary blood flow is markedly reduced. The collateral blood flow through intercoronary anastomoses is still more markedly decreased because of lowering of the interarterial pressure gradient. Opdyke and Foreman[14] also found that the coronary flow was reduced in shock.

Experiment II. Fluorescein Studies Showing the Effect of Shock on the Coronary Circulation.—

A. *Coronary Arteries Patent; Blood Pressure Lowered:* We have shown previously that the coronary circulation can be visually demonstrated in the

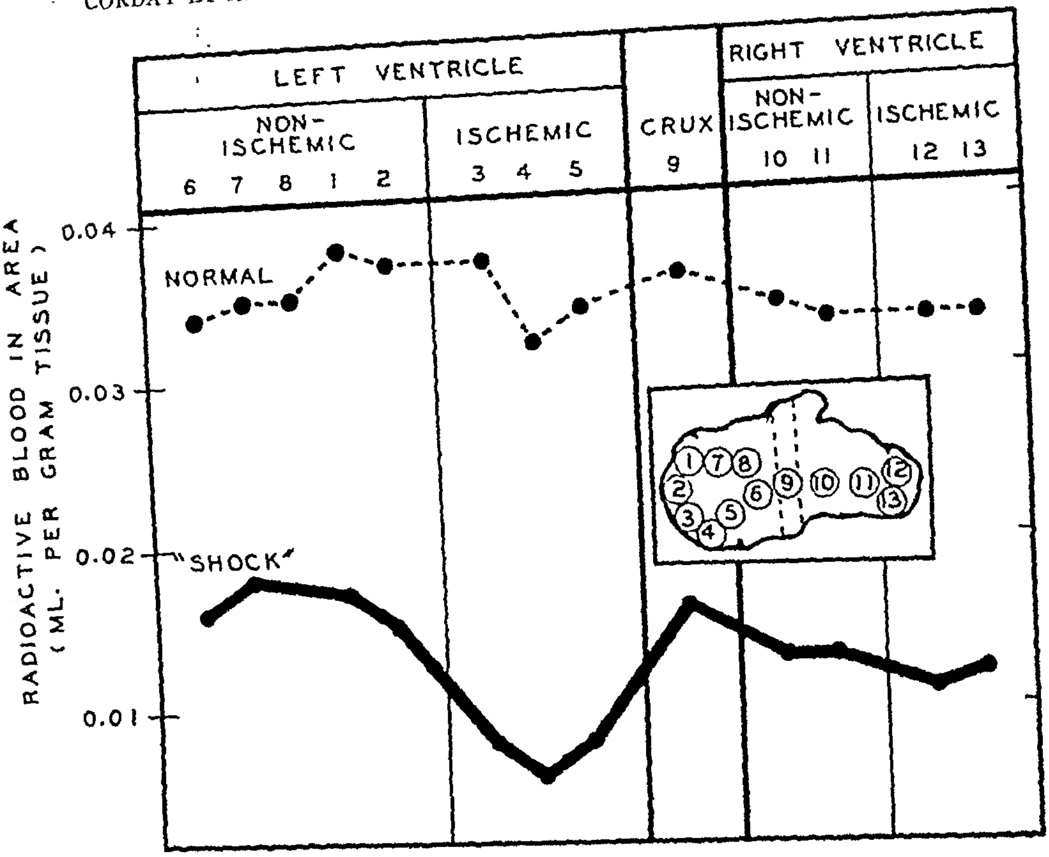

Fig. 2.—The average concentration of radioactive blood on the pericardial surface of hearts of twelve dogs with normal blood pressure is compared with that of nine dogs in shock with low blood pressure. Not only is the concentration of blood in the ischemic myocardium of "shock" dogs reduced, but more significant is the reduction in concentration of blood throughout the "shock" heart.

beating dog's heart by slow motion pictures (fifty frames per second) taken under special lighting which allows intravenously injected fluorescein to become visible. In animals with normal blood pressure, fluorescein appeared in the coronary arteries rapidly (within four to seven seconds) and in the next few seconds the entire heart became intensely fluorescent. This experiment was repeated on four dogs with low blood pressure induced by hemorrhage.

The appearance time of the fluorescein was greatly delayed, taking more than thirty-five seconds, and the rate of accumulation of fluorescein in the myocardium was greatly decreased. This was a visual demonstration of the diminution of the coronary blood flow in shock.

B. *Coronary Arteries Ligated; Blood Pressure Lowered:* It was shown previously in dogs with normal blood pressure and with ties in the middle of the anterior descending artery that fluorescein rapidly filled the ischemic region from contiguous areas.[9] The ischemic region generally became intensely fluorescent one to two seconds after the control region (Fig. 3,*A*). The experiment was repeated in six control dogs after the blood pressure had been reduced by hemorrhage as described in Experiment II,*A*.

Within thirty-five seconds, fluorescein appeared in all parts of the myocardium except that supplied by the ligated artery. In the latter region, it appeared after forty-five seconds but with much less intensity (Fig. 3,*B*).

A.

B.

Fig. 3.—*A*, Dog's heart with anterior descending coronary artery ligated. Blood pressure is normal. Photograph taken twenty-three seconds after fluorescein was injected into femoral vein demonstrates that fluorescein has completely filled the ischemic as well as the nonischemic myocardium via collateral circulation. In these black and white photographs, fluorescence appears white.

B, Dog's heart, anterior descending coronary artery ligated. Blood pressure is reduced by hemorrhagic shock. Photograph, taken eighty-six seconds after injection of the fluorescein, demonstrates that the myocardium supplied by the ligated vessel is only partially filled with fluorescein.

Experiment III. Effect of Shock on Myocardial Noncontractility.—

By means of slow motion pictures, it has been shown that the ischemic myocardium ceases to contract within three to four seconds after the coronary artery is ligated. This phenomenon, which has been known for many decades, has been studied by Tennant and Wiggers[15] and more recently in our laboratory.[16] We have done an extensive investigation on noncontractility in the ischemic region after coronary artery ligation.[16] Sometimes this phenomenon, which we have termed "ballooning," occurs only in late systole, but in other instances the ischemic region balloons during the entire systolic phase. After relatively small coronary arteries are ligated, the ballooning may not occur at all or may dis-

A.

B.

Fig. 4.—*A*, Dog's heart with anterior descending coronary artery ligated. Blood pressure is normal. Photograph taken in maximum systole demonstrates that the myocardium is contracting normally.

B, Same heart. Blood pressure now reduced by hemorrhagic shock. The myocardium supplied by the ligated artery now "balloons" outward in systole.

appear within one minute and then may come and go for unknown reasons. After ligation of large vessels, the ischemic region balloons more consistently. We have observed this inconstancy of ballooning in human subjects with coronary occlusion by means of roentgenkymograms.[16]

Method: Motion pictures were taken during and after ligation of the anterior descending artery in six dogs with normal blood pressure. The blood pressure was then reduced by hemorrhage to very low levels.

Results: The following significant changes occurred as a result of the low blood pressure (Fig. 4,*A* and *B*):

1. The ballooning became much more extensive in area and degree.
2. Cyanosis of the ischemic area became marked.
3. If ballooning had disappeared spontaneously, it reappeared and became more marked.
4. If there was only late systolic ballooning and not full systolic ballooning, it now occupied the full phase of systole.

Experiment IV. The Effect of Transfusion on Myocardial Noncontractility of Dogs With Coronary Artery Occlusion and Shock Blood Pressure Levels.—

In these experiments the blood was heparinized upon withdrawal and after fifteen to twenty minutes was administered intravenously into the same animals, raising the blood pressure to the prehemorrhage level. Motion pictures were again taken of the same hearts after transfusion. It was found that ballooning became less intense or disappeared entirely and the cyanosis also diminished or disappeared (Fig. 5,*A* and *B*).

Experiment V. Effect of Coronary Insufficiency on the Heart.—

In order that the effect of shock upon coronary sclerosis might be studied, the condition was simulated experimentally by constriction of the coronary arteries.

A. *Animals With Normal Blood Pressure*: The coronary arteries of six dogs were constricted by a ligature placed around the artery and a narrow glass tube about 0.25 mm. in diameter. The tube was then removed. It is estimated that, by this technique, the lumen of the artery was reduced at least 50 per cent, and in most cases, much more. For assurance that the artery was still patent fluorescein was injected into the femoral vein. If fluorescein entered the area supplied by the constricted artery as promptly as it entered the control areas, it was evident that the lumen was patent.

In view of the obvious clinical importance of coronary insufficiency and myocardial noncontractility, first we shall describe its effect on animals with normal blood pressure.

During the process of tying the artery around the glass cannula, the ischemic myocardium ballooned; but a few seconds after the glass rod was removed, the

A.

B.

Fig. 5.—*A*, Dog heart with anterior descending coronary artery ligated. Blood pressure reduced by hemorrhage. Photograph taken in maximum systole demonstrates that the ischemic myocardium is cyanosed and "balloons" outward (outlined by broken line).

B, Same heart as in *A*. Blood pressure now restored to normal by transfusion. The photograph taken in maximum systole demonstrates that the ballooning has disappeared and that the myocardium again contracts normally.

region supplied by the partially constricted artery resumed normal contractions and its appearance resembled that of the region before the tie was made. There was no cyanosis, and the region supplied by the constricted artery appeared to have a normal blood supply since fluorescein entered this region as rapidly and with as much intensity as the surrounding control regions.

This observation with fluorescein indicates that the circulation to the region supplied by the partially occluded artery is only slightly or not at all impaired. It was shown that when the lumen of the vessel is greatly narrowed, the blood supply may still be normal as determined by fluorescein filling. It must be concluded that arterial dilatation occurs and increases the blood flow to this region. Thus, under normal circumstances, with normal blood pressure and without excessive work, coronary narrowing is compensated for by arterial vasodilatation which maintains adequate blood flow and preserves myocardial contractility.

In view of the widespread incidence of coronary sclerosis with narrowing of the coronary arteries, the clinical significance of this finding is evident.

B. *Animals With Reduced Blood Pressure and Constriction of the Coronary Artery*: In the animals just described, the blood pressure was reduced by hemorrhage, and slow motion pictures were again taken. It was found that the region which was previously nonischemic and contracted well now ballooned in systole and became cyanotic.

C. *Effect of Transfusion in Coronary Insufficiency*: After the intravenous administration of heparinized blood, as described in the previous experiment, the contractility returned, the cyanosis disappeared, and the heart again appeared normal in all respects.

It is obvious that although the blood supply and contractility of the myocardium were normal while the blood pressure was normal, reduction in blood pressure caused a diminution in blood flow with loss of contractility. The deleterious clinical effect of low blood pressure on patients with coronary sclerosis and the therapeutic effect of agents which raise blood pressure, a clinical corollary of this experiment, will be discussed later.

Experiment VI. Electrocardiographic Changes After Hemorrhagic Shock.—

In order to simulate the effect of shock on the electrocardiograms of patients with coronary sclerosis, constricting ties, as previously described, were placed on the anterior descending branch of the coronary artery in two dogs, the mean blood pressure was greatly reduced by bleeding, and electrocardiograms were recorded. The electrocardiogram did not show significant changes after the constriction (Fig. 6,*A* and *B*). Blood was then withdrawn until the mean blood pressure dropped to 10 mm. of mercury. After ten minutes, electrocardiographic changes developed. T_1 and T_2 became deeply inverted, and the RS-T segment in Lead V_3 became depressed (Fig. 6,*C*). These changes persisted for twenty minutes until the animal was transfused with the heparinized blood which had been previously withdrawn. Within five minutes T_1 returned to normal, the inversion of T_2 lessened, and the RS-T segment in Lead V_3 became isoelectric (Fig. 6,*D*).

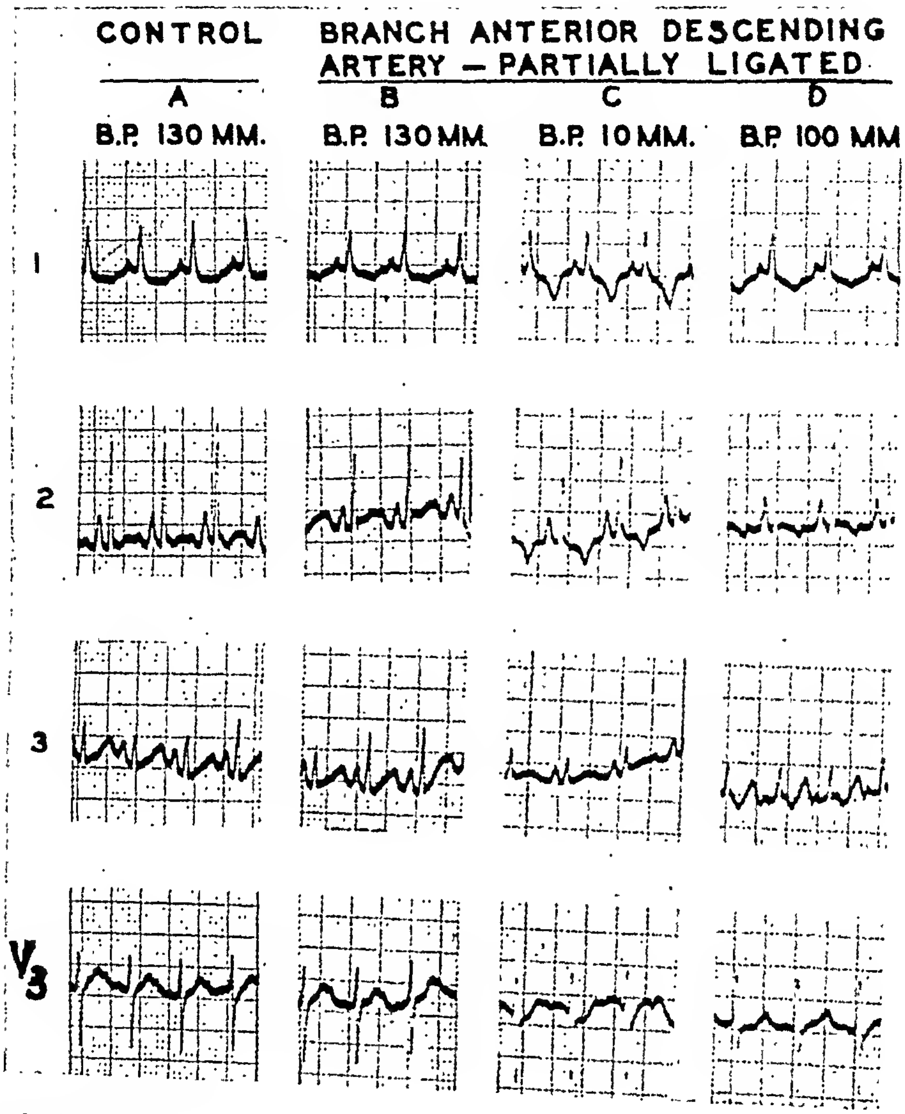

Fig. 6.—Electrocardiogram of dog.

A, Control electrocardiogram after pericardium was opened.

B, Electrocardiogram taken ten minutes after anterior descending coronary artery had been partially occluded. No significant change in the electrocardiogram.

C, Blood pressure now reduced by hemorrhagic shock. T_1 and T_2 are deeply inverted, T_3 is lower, and S-T segment in V_3 is depressed.

D, Blood pressure restored by transfusion. T_1 improved, T_2 less inverted, T_3 diphasic, and S-T segment in V_3 is isoelectric.

These changes are similar to those described by Master[17] as occurring in patients with coronary sclerosis who have sustained marked blood loss. They are due to the increased ischemia of the region supplied by the constricted artery resulting from the lowered blood pressure.

Experiment VII. Mechanism of the Lowered Blood Pressure After Coronary Occlusion.—

It is not the purpose of this paper to review the conflicting and inadequate evidence concerning the mechanism of shock which occurs after coronary occlusion in man. In at least forty dogs we have taken the blood pressure before, during, and after the ligation of large coronary arteries of the left ventricle. In some experiments we have ligated as many as eight major arteries of the left ventricle. In not a single dog, despite widespread loss of contractility, has there been a lowering of blood pressure for at least an hour or more after ligation of the arteries. If the mean blood pressure was low before the tie, as a result of hemorrhage and surgical shock, there was no further lowering after the artery or arteries were tied. The only time the blood pressure was reduced after a tie was when ventricular fibrillation supervened, in which case the blood pressure dropped rapidly to zero.

One may ask how these animal experiments differ from the dramatic shock-like state seen in patients after coronary artery occlusion.

In the dog, the pumping ability of the left ventricle does not appear to be impaired after coronary artery occlusion. Heart failure does not result since there is neither lowering of blood pressure, nor distention of the right ventricle, nor evidence of pulmonary edema. It would seem, then, that the shock state which occurs clinically is not directly due to heart failure.

It must be pointed out that the dog, the subject in these experiments, differs from man in several respects: (1) the dog is completely anesthetized; (2) the dog is completely atropinized; (3) in the dog, the remaining coronary arteries and myocardium are normal, whereas in human patients the nonobstructed coronary arteries may be the seat of advanced coronary sclerosis and there may be diffuse myocardial disease; and (4) of necessity the dog experiment is terminated in a few hours, whereas the patient may go into shock several days after the occlusion. The question of which of these reasons, if any, is responsible for the marked difference in behavior of the dog and man requires further study.

It is generally believed that shock with lowering of blood pressure and decrease in circulating blood volume is caused by one or two factors: (1) local fluid loss, and (2) visceral capillary atony.[18] After coronary artery occlusion in man, there is obviously no significant fluid loss into the ischemic region. It appears, therefore, that widespread capillary atony in both the general and pulmonary circulation is the most logical explanation for the development of shock. However, this capillary atony which may be the essential lesion in cardiac shock is difficult or impossible to demonstrate histologically.[19]

PART II. STUDIES ON THE TREATMENT OF SHOCK COMPLICATING CORONARY ARTERY DISEASE IN MAN

A. *Treatment of Shock in Acute Coronary Artery Occlusion.*—In view of our observations of the beneficial effect of treating experiment shock in the dog with coronary artery occlusion, we decided to apply vigorous treatment for the shock

of acute coronary occlusion in man. The treatment consisted of raising the blood pressure (1) by transfusion of whole blood or plasma or glucose solutions, and (2) by the administration of pressor drugs.

In simple uncomplicated cases without pulmonary edema we routinely administered intravenous plasma (treated with ultraviolet light to prevent hepatitis). Whole blood was used occasionally, especially in the presence of anemia. We feel that plasma is the fluid of choice because there is often hemoconcentration due to vomiting, diffuse sweating, and inanition. The use of saline or glucose parenterally seems less advisable because of the danger of pulmonary edema. If used, these solutions should be introduced slowly to prevent this complication. We used pressor amines, Neo-Synephrine, and epinephrine (1:1,000 solution), administering three to four minims of these substances every fifteen minutes. Caffeine and Coramine were also used. It should be clearly understood that these methods of treatment are experimental. The best method of treating shock after coronary artery occlusion is not known and is a practical problem worthy of extensive clinical and laboratory investigation.

It is of the greatest importance that while the patient is in shock the attending physician be in constant attendance to administer adequate but cautious treatment in raising the blood pressure and maintaining it at relatively normal levels.

If the patient had hypertension and cardiac hypertrophy previous to the occlusion, a systolic blood pressure of 110 or 120 mm. Hg after the occlusion may seem relatively normal. However, for that particular heart it is below the effective level and treatment should be instituted to raise it to approximately 150 mm. of mercury. If the blood pressure was normal before the occlusion, a systolic blood pressure of approximately 100 mm. Hg should be adequate. It should be recalled that the patient with acute coronary artery occlusion who is in shock is generally under profound sedation and the basal blood pressure of such patients is considerably less than when they are not under the influence of these drugs. For these reasons it is neither necessary nor advisable to raise the blood pressure to the patient's pre-existing normal blood pressure level.

The therapy should be instituted as soon as possible after shock develops. The longer the hypotension exists, the more coronary insufficiency and myocardial damage one can expect. Correction of severe hypotension after many hours or days of coronary insufficiency can be expected to produce myocardial failure, severe aneurysmal dilatation, or rupture of the heart. If the patient has been in shock for a long period of time, the prognosis is poorer and may be hopeless, because of irreversible changes. Myocardial rupture from the use of such therapy is unlikely if treatment is begun early, since rupture occurs from the tenth to twelfth day, by which time the patient is well out of shock.

Pulmonary edema is unfortunately a common occurrence after coronary artery occlusion and frequently occurs in patients with shock. Plasma or whole blood should be administered with caution, if at all, and the chief reliance must be placed on the pressor drugs. We have, however, not observed an accentuation of existing pulmonary edema in two cases in which plasma was administered.

The cause of pulmonary edema after coronary artery occlusion is not completely clear. The accepted explanation that it is due to left heart failure may be an oversimplification. In certain instances capillary atony, as it occurs in the toxemia of traumatic shock, may be an important element. The role of the central nervous system in the mechanism of pulmonary edema in patients is yet to be elucidated.[20]

We have treated many patients with shock by the methods which have been described, and in several instances the procedure has appeared to be life saving. Schwartz reported a similar case successfully treated.[21] Singer and Sampson[22] and Levine[23] have treated patients by transfusion with encouraging results. The following cases illustrate the usefulness of the treatment of shock after coronary artery occlusion. There have been failures, of course, but in no instance did the treatment appear deleterious.

CASE 1.—W. H. S., a 62-year-old man, was admitted to the hospital with dyspnea, profuse perspiration, and severe chest pain which had become progressively worse over a three-day period. His blood pressure at that time was 140/72. A diagnosis of myocardial infarction was made on the basis of electrocardiographic findings. He was put to bed and was given morphine for his pain and oxygen by nasal catheter. On the second day, the blood pressure was 125/90 and his pulse was rapid and thready. His breathing was still labored. The patient's condition gradually deteriorated and on the fourth day his blood pressure was unobtainable and his pulse rapid and irregular. The prognosis was considered grave.

He was given 1,000 c.c. of 5 per cent glucose in saline by intravenous infusion. Six hours later, his condition had improved remarkably, his pulse was regular, his blood pressure was 120/80, and he was no longer dyspneic. The patient's condition continued to improve in the next two days and his blood pressure remained above 118/78. A pericardial friction rub developed on the eleventh day, but the patient's subsequent course was uneventful and he fully recovered.

CASE 2.—S. H., a 54-year-old man, was admitted to the hospital in profound shock; he had complained previously of severe precordial pain. The patient's color was good, the skin was cold and moist, and the blood pressure could not be obtained. The patient was given 300 c.c. of plasma and 5 minims of epinephrine subcutaneously, and then was placed in an oxygen tent. Two hours later his blood pressure rose to 110/90 and his condition had improved somewhat, but he remained unconscious. An electrocardiogram revealed recent posterior myocardial infarction.

Blood pressure readings were made every hour. The morning of the second day his blood pressure was 90/70. In the next three-day period, the systolic blood pressure varied between 80 and 110 mm. of mercury. Whenever the blood pressure dropped below 90, as it did on five occasions in this period, 3 minims of epinephrine, 1:1,000, were administered. On the fourth day his condition again appeared to be very critical; he was in profound shock and his blood pressure remained below 90 mm. of mercury. He was given 300 c.c. of plasma and 1.0 c.c. of Coramine twice on that day. Following this, his blood pressure rose to 110 to 130 systolic, and his condition improved dramatically. On the fifth day he regained consciousness and for the next four days his ondition was most satisfactory.

On the tenth day, however, the patient developed persistent paroxysmal auricular tachyardia. Despite all measures to break this arrhythmia, it continued for four days; the patient's ondition deteriorated; and he died as a result of the arrhythmia.

CASE 3.—W. S., a 43-year-old man, was admitted to the hospital for treatment of hypernsion. He complained of headaches and dizziness of two years' duration. Blood pressure on dmission was 250/170 and the eye grounds revealed a Grade III retinopathy.

Left-sided sympathectomy was performed on July 14. After the operation the patient's lood pressure dropped to 120/90; the night of the operation there was further drop to 88/70.

The patient remained in a state of vascular collapse and at 4:30 P.M., July 15, he complained of severe precordial pain and his nail beds were cyanotic. At 7:15 P.M. he became markedly cyanotic and the electrocardiogram showed changes characteristic of a posterior myocardial infarction. At 11:00 P.M. the blood pressure had dropped to 60/40. The patient was unconscious and pale and his pulse was weak and thready. There appeared to be little hope of his surviving. At this time he was given a transfusion of 300 c.c. of plasma and within one hour the blood pressure rose to 118/80, at which level it remained all night. On the morning of July 16, he was again transfused with 300 c.c. of plasma and the blood pressure rose to 130/90. The patient's condition was markedly improved; cyanosis had disappeared, but he complained of precordial pain. Râles were present in both lung bases. The patient developed a pericardial friction rub on July 18. His blood pressure remained above 130/90 and his subsequent course and recovery were uneventful.

B. *Shock and Coronary Insufficiency.*—When shock of extracardiac origin occurs in patients with coronary sclerosis, electrocardiographic changes may develop.[17] After adequate transfusion, the electrocardiogram returns to normal.[23]

We demonstrated in Experiment VI that when shock occurs in a dog with a constricted coronary artery, the region supplied by that artery ceases to contract and balloons outward, becoming similar to the myocardium with complete arterial occlusion. In this experiment, electrocardiographic changes indicative of coronary insufficiency also occurred. When the blood pressure was restored in these animals by transfusion, the myocardial ballooning, cyanosis, and electrocardiographic changes disappeared. These observations and our knowledge of the mechanism of the collateral circulation of ischemic myocardium have led to a better understanding of so-called coronary insufficiency in man. The recent work of Blumgart,[24] Master,[25] and Levy[26] has contributed greatly to our knowledge of the subject. We have observed patients who developed electrocardiographic changes of severe coronary insufficiency after hypotension from surgical and hemorrhagic shock. The excellent therapeutic results of the treatment of shock in these cases appear to confirm our work on the effect of shock on the coronary circulation in dogs with partial coronary occlusion. It has been demonstrated repeatedly that patients and animals with very low blood pressure may develop electrocardiographic changes characteristic of myocardial insufficiency. This is especially true if there has been antecedent coronary artery disease, and is illustrated in the following cases:

CASE 4.—C. T., a 54-year-old man with known arteriosclerosis and moderate hypertension, was operated upon for the removal of a renal calculus. An electrocardiogram taken the day prior to surgery was normal. Spinal anesthesia was given. Afterward, the blood pressure gradually fell to 90/60. The anesthesia record showed the blood pressure remaining at this level for the duration of the surgery, approximately one and one-half hours. No pressor drugs were administered during this period. In anticipation of coronary insufficiency as a result of the prolonged lowered blood pressure, an electrocardiogram was taken immediately upon the patient's return to his bed. There was elevation of the RS-T segment with diphasic T waves in Lead V_2, and T_1 was flattened. The patient at this time was still under the effect of the morphine and anesthesia but was perspiring and had a rapid pulse.

Treatment by infusion of glucose in saline was cautiously administered and the systolic blood pressure soon rose to 150 mm. Hg, where it was maintained. The next morning another electrocardiogram was taken and the changes of the day before had disappeared entirely. The pattern was now similar to the original tracing. The patient made an uneventful recovery from his operation and there were no cardiovascular complications.

CASE 5.—J. M., a 62-year-old man, debarked from a plane with acute pulmonary edema after flying for many hours at high altitudes without oxygen. In previous years he had sustained two myocardial infarctions and was taking 0.2 mg. digitoxin daily. A few hours after the onset of pulmonary edema, his blood pressure dropped from 120 mm. to a level at which it could not be obtained. His skin was pale and cold and he perspired profusely. Dyspnea was marked and he was pulseless. His pulmonary edema improved with the shock state, but it was felt that he would surely expire. In view of the fact that he had such a poor coronary circulation, it was reasoned that his blood pressure should be raised or myocardial damage would result.

The patient was promptly given 5.0 mg. Neo-Synephrine and 2.0 c.c. Coramine intramuscularly and oxygen by mask. The blood pressure rose within a few minutes, but on several occasions the systolic pressure dropped below 95 mm. of mercury. By means of repeated injections of epinephrine and Coramine, the blood pressure was sustained for two hours and then it remained above 110 mm. of mercury. His condition improved gradually until it appeared that he would survive. His pulmonary edema did not recur and his subsequent recovery was dramatic.

DISCUSSION

It was shown in these experiments that the coronary circulation of animals with coronary occlusion and reduced blood pressure differs in two important respects from that of animals with coronary occlusion and normal blood pressure: (1) there is a significant reduction in the collateral blood supply to ischemic portions of myocardium, and (2) there is a significant reduction in the blood supply to other (control) parts of the myocardium. These observations were made in both the radioactive red blood cell experiments and the fluorescein experiments.

Decreased Circulation to the Ischemic Myocardium.—In the animals with reduced blood pressure the decreased circulation to the ischemic region is obviously due to the reduced pressure gradient. The pressure in all the vessels of the ischemic region is very low in both normotensive and hypotensive animals. But in normotensive animals the pressure in the accessory coronary arteries is high enough to force abundant blood into the ischemic region in a relatively short time. In hypotensive animals, however, the pressure in the nonobstructed coronary arteries is also low and the collateral blood flow into the ischemic region is greatly reduced.

Since the collateral blood supply to the ischemic region nourishes the ischemic myocardium, promotes healing, and reduces the size of the infarct, decreased filling such as occurs in shock would be expected to have a deleterious effect upon ischemic myocardium. One would therefore expect the incidence of cardiac rupture to be greater in patients who have been in shock for some time, since under this circumstance necrosis and myocardial weakening could have progressed. In addition, the incidence of aneurysmal dilatation of the ischemic region in the left ventricle may be less in patients in whom shock had not been present.

Decreased Circulation in Nonischemic Myocardium.—The observation that with low blood pressure there is a reduced circulation in regions of myocardium supplied by nonoccluded arteries is probably even more significant than the observation of diminished collateral blood flow to the ischemic myocardium. This was found in both the radioactive red blood cell and fluorescein experiments.

It should be pointed out that the nonobstructed coronary arteries in the dog are normal, whereas in patients with coronary disease there is usually present more or less occlusive vascular changes in the nonobstructed arteries. Therefore, the effect of hypotension on the so-called nonischemic portions of the left ventricle in patients with coronary occlusion is more marked (with more significant reductions in blood flow) than in dogs with an equivalent reduction in blood pressure. Thus, in patients with shock, not only does the region supplied by the occluded vessel have a diminished blood flow, but there are probably significant degrees of ischemia in large segments of myocardium, the major arteries of which are not completely occluded. This could also account for the myocardial necrosis found in nonischemic regions in patients in shock, described by Blumgart,[24] and the subendocardial necrosis more recently described by Master and his co-workers.[17] The finding that the blood flow to nonischemic regions of the left ventricle is reduced offers an explanation for the myocardial insufficiency referred to earlier.[1-7]

It has been claimed by others that coronary insufficiency does not occur during the hypotension following shock. The reason given is that the work of the heart is reduced in proportion to the reduction of coronary blood flow. This concept is not substantiated by our experiments on shock in both animals and human subjects. In dogs, increased ballooning and increased cyanosis were seen as a result of the shock state. In man, electrocardiographic changes indicative of coronary insufficiency were observed with shock. If the reduced work of the heart were actually a means of compensating for coronary insufficiency, these signs would not appear.

Myocardial Contractility and Shock.—In both man and the experimental animal it has been demonstrated that the region of myocardium supplied by an occluded artery may become noncontractile. Detailed studies of noncontractility in ischemic myocardium have been made in this laboratory.[16] Although the mechanism of noncontractility is not known, it was shown that it is related to, and occurs as a result of, ischemia and anoxia. In the present study it was shown that in dogs with partial occlusion of the coronary arteries, contractility of the involved myocardium remained normal. When the blood pressure was reduced, the region supplied by the constricted vessel ceased to contract and ballooned markedly. This observation is of the greatest clinical importance, since patients who have myocardial infarctions from coronary artery occlusion usually have generalized coronary sclerosis and narrowing of other coronary vessels. Thus, as in the experimental animal, the reduction of blood pressure resulting from a coronary artery occlusion in man probably results in noncontractile regions of myocardium where there is coronary sclerosis but no occlusion. As shock becomes more intense in such cases, the noncontractile region should become more extensive. This sequence of events would exert a severe strain upon the remaining contractile portion of the left ventricular myocardium, particularly as the nourishment to this portion is also reduced. The persistence of this situation must result in death, and its occurrence may well serve to explain the fact that the mortality after coronary artery occlusion is increased if shock is a complicating factor. Whether the terminal arrhythmia is ventricular fibrillation or

ventricular asystole, as a result of the grossly altered mechanics, is of minor importance. Unless efforts are made to correct the fundamental defect, it seems useless to administer a drug such as quinidine in an attempt to prevent ventricular fibrillation in a heart with large noncontractile regions and with only a small portion of ischemic left ventricle contracting.

From the experimental evidence that has been obtained in this study, it would seem that as long as the blood pressure remains normal there is apparently normal coronary blood flow, with resulting normal myocardial contractility and absence of both cyanosis and electrocardiographic changes. This may be the result of vasodilatation of the vessels in the involved region, which maintains the normal blood flow despite a marked reduction in the lumen of a coronary artery and a reduced pressure gradient distal to the stenosis. It is also possible that the blood flow to the potentially ischemic region is enhanced by the intercoronary arterial anastomoses because the pressure in these anastomoses which are supplied by nonobstructed arteries is higher than the pressure in the constricted artery. Possibly the persistence of this pressure gradient in the interarterial anastomoses and the increased blood flow through them constitute a stimulus for their gradual enlargement.

In view of the widespread existence of coronary sclerosis in a large proportion of adults in the fifth to seventh decades, the significance of this observation cannot be overemphasized. As long as the blood pressure remains normal, the blood flow to the potentially ischemic region may remain normal because of vasodilatation and the gradual enlargement of the existing intercoronary anastomoses which are of great value when the closure finally becomes complete. The intercoronary anastomoses which become prominent during the many years of partial ischemia may well save the patient's life. As Blumgart[27] has shown, these intercoronary anastomoses may be large enough to prevent tissue necrosis, so that the final closure may be completely silent and unaccompanied by clinical signs or electrocardiographic changes.

If the blood pressure is reduced, the region of myocardium supplied by the constricted artery loses its ability to contract and becomes cyanotic. Electrocardiographic changes indicative of myocardial ischemia occur under these circumstances. Since stenosed arteriosclerotic coronary vessels are more frequently observed in individuals in the older age groups, it is particularly important to prevent and treat the shock and low blood pressure which may result from surgical operations, anesthesia, accidents, hemorrhage, infections, intoxications, burns. Such older patients die not only from the direct effects of shock but from irreparable secondary damage to the heart. In the experimental animal the heart improves rapidly when the blood pressure is elevated; the ballooning disappears and the electrocardiographic changes regress or disappear. Careful observation of the heart in magnified, slow-motion pictures taken soon after the elevation of the blood pressure shows that it is transformed from a malfunctioning, cyanotic organ into a mechanically efficient and apparently normal organ.

Treatment of Shock.—It is obvious that in many patients in shock, with coronary occlusion, the organic damage to the heart is so severe that death is

inevitable, regardless of the treatment. Likewise, there are undoubtedly some patients with relatively mild shock who recover without any specific treatment of the shock. Between these two extremes there is a variable number of cases in which the treatment of the shock may be a life-saving procedure. Although the final purpose is to restore the blood pressure and thereby improve the coronary circulation, the best method of achieving this aim is still to be worked out. Enough is known, however, to allow the physician to do all that he can by methods available to everyone to elevate the blood pressure and thus preserve the myocardium.

The treatment of shock after coronary artery occlusion now appears to rest on a firmer clinical basis. From the experiments done under controlled conditions in experimental animals, there is strong indication for vigorous and intelligent treatment which may indeed be spectacular. Since the mechanism of the shock which follows coronary artery occlusion is unknown, the most desirable treatment to raise the blood pressure is more or less empirical at the present time. In our experience, the use of plasma and blood and the careful use of the pressor amines have appeared to be life saving in a few selected cases. Since shock does not occur in the animal with experimental coronary artery occlusion, the problem can be answered only by means of carefully controlled clinical studies which, we hope, will more clearly define the exact therapeutic procedure indicated in any particular case.

It has been thought that the work of the heart is reduced as a result of the decreased blood pressure and that the low blood pressure should not be treated.[8,9,10] But in patients with antecedent diffuse coronary disease and with hypertrophied left ventricles, the coronary flow may be suboptimal with preexisting blood pressure levels. Lowering of the blood pressure in such patients, although it may reduce the work of the heart, seems to cause an increased myocardial insufficiency, and actual tissue necrosis has been observed histologically in such cases.

Heart failure rarely occurs in dogs after experimental coronary occlusion, but it frequently occurs after coronary artery occlusion in man. The myocardial insufficiency in dogs is probably insignificant because the nonobstructed coronary arteries are normal. In man, however, the generalized coronary artery disease probably results in more generalized myocardial ischemia during hypotension, and this may explain the heart failure which sometimes follows small or moderately large myocardial infarctions.

The danger that myocardial rupture may result from the early use of therapy to raise the blood pressure is probably overemphasized, because rupture generally occurs only on about the tenth to fourteenth day after coronary occlusion.[28] Raising the pressure at this time could easily cause rupture of the myocardium, because tissue necrosis has already occurred. It is possible that the early elevation of the blood pressure would prevent tissue necrosis and allow for better healing of the ischemic regions, thereby preventing the myocardial necrosis which is the cause of ventricular rupture.

Coronary occlusion is common in patients with hypertension. In such cases the blood pressure may fall markedly and be insufficient for the hypertensive

patient with cardiac hypertrophy, despite the fact that the blood pressure does not fall below levels considered to be normal in the normotensive patient. Patients with markedly hypertrophied left ventricles caused by hypertension, who have a so-called normal blood pressure after coronary occlusion, should be treated as though they were in shock. Hypertensive patients without marked left ventricular hypertrophy may be treated more conservatively. Sedation alone causes reduction in the blood pressure of hypertensive individuals. Therefore, it should be emphasized that the therapy that is being recommended applies to patients with pronounced lowering of the blood pressure and that such therapy must be administered with caution. For instance, if the systolic blood pressure before coronary occlusion had been maintained around the level of 220 and it dropped to 110 mm. Hg after occlusion, it should probably be raised to about 150 mm. Hg, if possible.

In unpublished observations from this laboratory, it was found that the rate of absorption of subcutaneously administered materials can be quantitatively and simply determined by means of radioactive isotopes. It was found, in experimental animals, that the absorption was greatly delayed after hemorrhage and improved after transfusion. There are clinical applications of these experimental observations. Occasional patients in shock, after coronary occlusion, still have severe substernal pain. The usual rule is that these patients receive ¼ grain morphine sulfate every fifteen minutes subcutaneously. This procedure may be illogical, for two reasons. The patient may receive little relief, since only a small fraction of the drug may be absorbed from the site of local injection. This may result in repeated injections for the production of an effect. Then, if the blood pressure should become elevated spontaneously or as a result of specific treatment, the large unabsorbed depot of morphine may be rapidly absorbed and death may result from an overdose of morphine.

Our knowledge of the mechanism of traumatic and surgical shock is much more advanced than our knowledge of shock after coronary occlusion. Furthermore, it is known that shock is not a distinct entity and may result from a variety of causes which require different treatment. It is possible that the shock which follows coronary occlusion also results from a variety of causes. Such causes may include (1) reflex influences, (2) mechanical factors, or disturbed dynamics, (3) toxic effects, as from myocardial necrosis, or (4) combinations of these factors. Boyer[30] has thoroughly reviewed the subject of cardiogenic shock. As a result of extensive experimental investigation on shock from wounds, burns, infection, and certain types of intoxication,[7,18,19,29] we feel that the factor of capillary atony should be carefully considered. Obviously there are many types of shock, and after coronary artery occlusion more than one factor may be responsible for the capillary atony which may well explain the hypotension.

The ideal treatment in any individual case should depend upon the cause, and until further knowledge is obtained on the factor or factors causing shock, after coronary occlusion, the treatment must remain largely empirical. Regardless of the mechanism of the shock, however, the results of our experiments show that it is of great importance promptly to overcome extreme hypotension which is associated with coronary occlusion or which occurs in coronary insufficiency.

CONCLUSIONS

1. A series of experiments has been performed to study the effect of shock, with or without coronary artery occlusion, on the coronary circulation and on myocardial contractility.

2. The first method consisted of the intravenous injection of radioactive erythrocytes into dogs with ligated coronary arteries and marked reduction of blood pressure induced by hemorrhage.

3. It was found that with low blood pressure levels the coronary blood supply in nonobstructed vessels was greatly reduced, as was that through the collateral intercoronary anastomoses.

4. In slow-motion pictures of the heart, special lighting allowed intravenously injected fluorescein to become visible after it reached the coronary arteries. In confirmation of the observations made with the radioactive red blood cells, this method also showed that the coronary circulation is greatly diminished in shock. With reduced pressure gradient through interarterial anastomoses, the blood supply to regions made ischemic by ligation of coronary arteries was much less than in animals with normal blood pressure.

5. After coronary artery ligation, the region supplied by the ligated artery usually lost its contractility and ballooned outward during systole. With the production of shock, the region of noncontractility became much more extensive and the ischemic region became more cyanotic. Electrocardiographic changes indicative of myocardial ischemia occurred.

6. After transfusion of heparinized blood, contractility of the ischemic region improved, cyanosis decreased, and electrocardiographic abnormalities regressed or disappeared. This was the result of the improved nutrition via the collateral circulation to the region normally supplied by the ligated artery.

7. Constriction of the lumen of the coronary arteries, simulating coronary sclerosis, affected neither contraction nor color of the potentially ischemic region while the blood pressure was normal. The coronary blood flow appeared to be normal according to the inflow of fluorescein in this region. The normal blood flow resulted from vasodilatation in the potentially ischemic region and the increased flow through interarterial anastomoses maintained by the intercoronary pressure gradient. These observations explain normal myocardial function in the older age group with coronary sclerosis.

8. If the blood pressure was lowered in animals with partial coronary ligation, contractility was diminished or absent and the entire heart, especially the ischemic region, became cyanotic. After blood transfusion and restoration of normal blood pressure, normal contractility returned and cyanosis disappeared.

9. These observations on coronary blood flow and noncontractility explain on a physiologic basis "coronary insufficiency" or "coronary failure." Our observations offer good physiologic reasons for correcting shock and low blood pressure due to various causes in the older age groups.

10. The mechanism of clinical shock following coronary artery occlusion is unknown. In dogs, there is no lowering of blood pressure, evidence of left heart failure, or pulmonary edema following extensive ligations of many of the coronary arterial branches of the left ventricle.

11. As a result of the experimental observations in patients with shock after coronary artery occlusion, one may reasonably believe that there exist regions of noncontractility in the myocardium. If noncontractility becomes sufficiently extensive, death is inevitable. In this state of shock, a small functioning segment of the myocardium of the left ventricle has a greatly reduced blood supply, yet is called upon to do the work of the entire left ventricle.

12. The low blood pressure of shock, after coronary artery occlusion, must be vigorously, intelligently, and immediately treated. In a few cases, it was demonstrated that intravenous plasma, whole blood, and the judicious use of pressor drugs may prove to be life saving.

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THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF THE DISTURBANCES OF THE HEART'S VENOUS CIRCULATION

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THE construction and function of the venous system of the heart are still not known in all their details. According to our present knowledge, the blood which reaches the heart through the arterial system leaves the myocardium in five different ways: (1) through the capillaries into the veins of the heart and thence through the coronary sinus into the right atrium; (2) through the capillaries into the Thebesian veins and thence into the ventricular cavity; (3) through the so-called luminal arteries directly into the ventricle; (4) from the so-called sinusoid arteries through the myocardial sinuses into the ventricular cavity; and (5) through extracardiac anastomoses, and thence indirectly into the main venous system of the body.

In case the coronary arterial blood is interfered with in its return to the heart, venous congestion occurs. The question to be considered is whether congestion of the myocardium, resulting from disturbance of the venous circulation, produces anatomic or functional changes in the heart muscle, and if so, whether this is revealed by the electrocardiogram.

Laufer,[6] after tying the coronary sinus, did not observe any change in the ventricular muscle, but did observe some degree of fibrosis in the atrial muscle. The animals used in these experiments withstood the obstruction of the sinus very well. These experiments seemed to support Condorelli's[3] opinion that venous congestion of cardiac muscle only injures the atrial muscle. From the electrocardiographic point of view, the problem was studied by several workers[1,4,8] who found that obstruction of the coronary sinus produced either no change or only a moderate change in the size or direction of the T wave.

I did not think it likelythat venous congestion could exist without causing ›me characteristic electrocardiographic change. I based my opinion on two ›nsiderations: one was the fact that the electrocardiogram is extremely sensitive › disturbances of the arterial circulation to the heart. It did not seem probable ıat disturbance of the venous circulation could be present without exercising ny effect. The other fact was the capacity of the heart's venous circulation; would seem to be so abundant in order to insure against the possibility of the

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Editor's Note.—The experimental observations reported in this paper were to have been presented a Plenary Session of the Third Inter-American Cardiological Congress, Chicago, Ill., June 13-17, ›48. Unfortunately, the author found it impossible to attend the Congress.

development of venous congestion. I could not believe, therefor, that if disturbance of the venous circulation develops this would not injure the ventricular muscle and affect the electrocardiogram. My conviction was proved by the results of experiments on animals.

EXPERIMENTAL METHOD AND RESULTS

In order to produce venous congestion, I partially or completely obstructed the coronary sinus, since it seemed likely that this procedure would produce disturbance of venous circulation in the whole heart.

The technical part of the experiment consisted of partially or entirely tying off the coronary sinus of a dog's heart almost immediately before its entrance into the right atrium. After tying off the sinus I observed the heart muscle for one hour or more and recorded electrocardiograms (three standard limb leads and Lead CF_4) every five minutes.

Within a few minutes after tying off the coronary sinus one could observe the ventricular muscle becoming somewhat cyanotic; it maintained this shade through the whole experiment. Shortly after removal of the ligature from the coronary sinus, the heart muscle recovered its natural color.

An essential change was observable in the serial electrocardiograms. In all three limb leads and in the chest lead as well, the amplitude of the QRS complex slowly and gradually decreased. The maximum reduction in voltage developed ten to thirty minutes after the obstruction. The variation in the time of development of the maximum change most likely depended upon whether the coronary sinus was obstructed entirely or only partially. In any event, as a consequence of venous congestion of the myocardium, low-voltage QRS complexes developed in the electrocardiogram.

Two types of low-voltage complexes could be distinguished. In the type which I call the *R Type*, the R wave becomes smaller (Fig. 1). In the other type, which I call the *S Type*, in addition to the R wave becoming smaller, a more or less deep S wave appears (Fig. 2).

Except for the development of low voltage of the QRS complex, the electrocardiogram is not greatly affected. The P wave is not essentially changed, though it usually becomes somewhat higher in the three limb leads. The RS-T segment remains on the isoelectric line during venous congestion. In some cases the T wave shows no change, but in most cases this wave becomes lower or even inverted.

After removal of the ligature from the coronary sinus which thus relieves the venous congestion, all electrocardiogram deviations usually disappear within ten to twenty minutes.

DISCUSSION

As the result of my animal experiments, I have concluded that venous congestion of the myocardium which results from the tying off of the coronary sinus harms the heart muscle as a whole. This is shown not only by the development of low-voltage QRS complexes but also by the pathologic changes which the

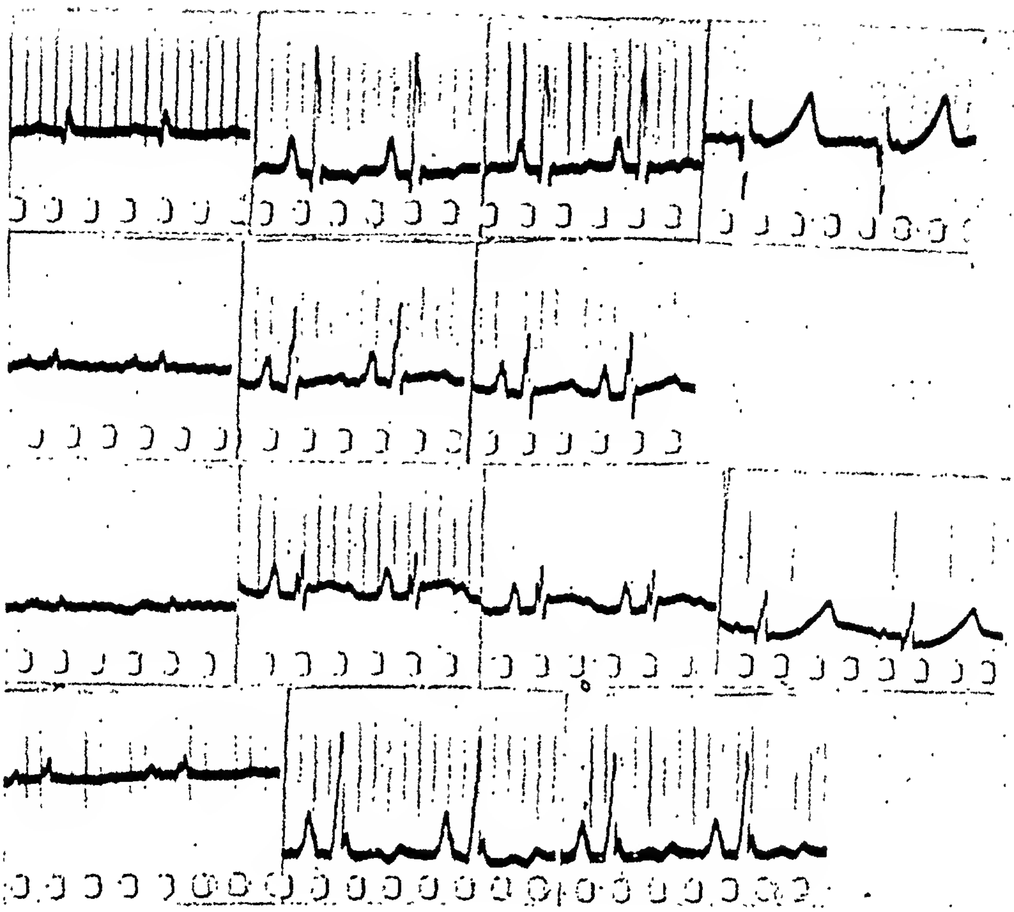

Fig. 1.—*A*, Leads I, II, and III and a lead similar to Lead CF_4, in a dog. *B*, The electrocardiogram made ten minutes after the tying off of the coronary sinus. *C*, Electrocardiogram made twenty minutes after the tying off of the coronary sinus. *D*, Electrocardiogram made ten minutes after removal of the ligature from the coronary sinus.

The tracings clearly show that obstruction of the coronary sinus causes the QRS complex to become smaller in the limb and chest leads. Since the low voltage results from lowering of the height of the R wave, this is the *R Type of pathologic low voltage.* (See text.)

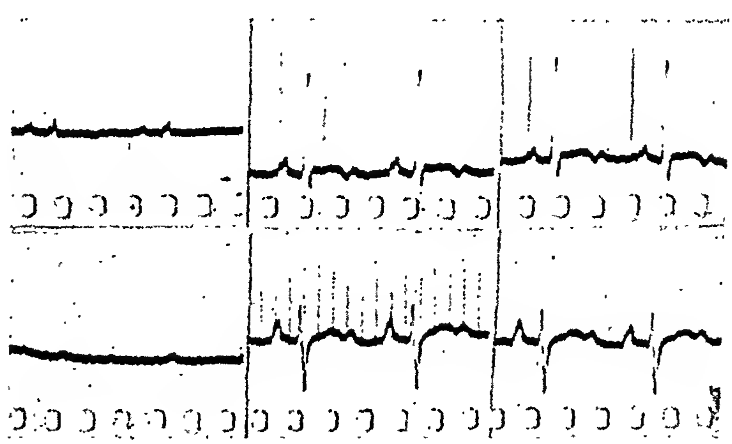

Fig. 2.—*A*, Leads I, II, and III of a dog. *B*, Electrocardiogram made thirty minutes after the ying off of the coronary sinus.

The figure clearly shows that the QRS complex becomes smaller as the result of the tying off of he coronary sinus. This is an example of the *S Type of pathologic low voltage;* the R wave becomes ower and an S wave becomes larger. (See text.)

T wave undergoes. On the basis of my experiments I feel justified in stating that the pathologic low-voltage electrocardiogram is just as characteristic of disturbance of the venous circulation of the heart as is the electrocardiogram with typical patterns for obstruction of the arterial circulation.

I do not wish to discuss further the implications of these experimental results at this time. In another article I shall attempt to deal with other phases of the subject, including the application of the results of my experiments to human pathology, including myocardial infarction, mitral stenosis, and other lesions.

SUMMARY AND CONCLUSIONS

1. Venous congestion injures the ventricular muscle.
2. As a result of the injury produced by venous congestion, pathologic electrocardiographic changes develop.
3. In these abnormal electrocardiograms, low-voltage and pathological changes of the T wave are striking and consistent. For this reason I have called the pattern, "pathological low-voltage."
4. With the disappearance of venous congestion, the pathologic electrocardiogram, and therefore the abnormal state of the ventricular muscle, return to normal within a short time.
5. I consider that the pathological low-voltage pattern is just as characteristic of venous congestion of the myocardium as the electrocardiogram with certain typical findings is characteristic of obstruction of the arterial circulation.

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THE GRAPHIC REGISTRATION OF BASAL DIASTOLIC MURMURS

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The high-pitched blowing diastolic murmur heard most characteristically in slight aortic regurgitation is at times extremely faint, and the most careful auscultatory technique is necessary for its detection. The decision as to the presence or absence of such a murmur is of the greatest importance, for clinical experience has indicated that the diagnosis of aortic insufficiency is unwise unless the presence of the murmur can be established without a doubt. The usual auscultatory technique cannot be depended upon when the loudness of the murmur borders on the average threshold of human hearing, and as a result, differences of opinion arise even among the most competent clinicians.

The development and commercialization of the modern electronic phonocardiograph led to its application to the detection of faint aortic diastolic murmurs with the hope that instrumentation would provide a more positive method for their detection. However, it was found that the usual commercial phonocardiograph was unsuitable, in that it often failed to register the faint, high-pitched murmur although its presence was well established by auscultation.[1,2] On the other hand, it was observed that low-pitched sounds and murmurs, such as the auricular sound, the third sound, and the mitral diastolic murmur, all of which lie at the opposite extreme of the auscultatory spectrum, were registered distinctly even though they were at times inaudible.[3,4,5] The impression was thus created that faint, high-pitched murmurs cannot be registered phonocardiographically, although they are audible on careful auscultation with the acoustic stethoscope. As a result of this concept, there has been no satisfactory study by phonocardiography of the basal diastolic murmurs.

Our observations indicate that failure to register the faint, high-pitched basal murmurs has been caused by several factors. The first of these is that the phonocardiograph may have insufficiently high sensitivity and insufficiently high deflection speed to record these murmurs. Second, the instrument may not provide sufficient attenuation of the lower frequency vibrations in comparison with the vibrations of higher frequency. If this is the case, it is impossible to use sufficient amplification to register the higher frequencies because the lower frequency vibrations will then have such a large amplitude as to make satisfactory recording and analysis of the tracing impos-

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sible. Third, the physical and physiological factors that are involved in the production of such murmurs may not be properly understood. Finally, failure to register these murmurs may be due to an imperfect phonocardiographic technique.

It is of greatest importance in phonocardiography that the response of the instrument used with respect to the different frequencies be both understood and clearly stated. This means that the accentuation or attenuation of the intensity of vibrations with regard to their frequency should be placed on record. It is only in this manner that tracings taken with different instruments can be interrelated. A study of heart sounds and murmurs by means of calibrated phonocardiography has recently been made by Mannheimer.[6] He has used six channels, recording vibrations in six separate, but overlapping, frequency bands. Each of these channels has a linear response, which means that the intensity of the vibrations is not accentuated or attenuated with regard to their frequency. It is interesting to observe the considerable difference in the configuration of the sounds and murmurs, even in adjacent frequency bands. Indeed, some murmurs recorded in one band cannot be identified in the adjacent band. This marked difference illustrates the danger of drawing any conclusion about the configuration of sounds and murmurs, or even about their presence or absence, from tracings taken with phonocardiographs in which the frequency response is not known. The calibrated phonocardiograph fulfills the requisites of proper statement and description of frequency response characteristics and is a useful instrument for harmonic analysis. It is difficult, nevertheless, to correlate the tracings with what is heard on auscultation.

The phonocardiograph most satisfactory for correlation with auscultatory findings is an instrument in which the various frequencies of the auscultatory spectrum undergo the same modification with regard to intensity as occurs with the average acoustic stethoscope, together with that of the average human hearing mechanism. In this way the graphic representation most approximately parallels the auditory impressions obtained on auscultation. In addition to a frequency response of this character, it is desirable to be able to use an alternative frequency response in which there is less relative attenuation of the lower frequencies. This will enable the registration of the lower frequency components of audible and subaudible sounds and murmurs. We have therefore used in this study the Sanborn Tribeam phonocardiograph, with stethoscopic and logarithmic microphones and interchangeable chestpieces.[3,4]

The purpose of this paper is to analyze the physiological and physical factors which are involved in the production of the basal diastolic murmurs, to present a phonocardiographic technique which has proved satisfactory in their reproduction, and to describe the graphic configuration of these murmurs. We have included in this study murmurs due to aortic and pulmonary regurgitation, together with a discussion of tracings showing diastolic vibrations where no murmur was heard. Patients with continuous murmurs from patent ductus arteriosus, arteriovenous aneurysm, and venous hum have been excluded.

PHYSIOLOGICAL AND PHYSICAL CONSIDERATIONS

The murmurs of aortic and pulmonary regurgitation result from the backflow of blood from the great vessels into the heart during the diastolic phase of the cardiac cycle. This is usually due to deformity of the value cusps which may vary in extent, even to retroversion or perforation of the cusps. It may be due, however, simply to a dilatation of the aortic or pulmonary ring and under these circumstances be reversible. Occasionally regurgitation may commence with the occurrence of vegetations on a valve that previously functioned normally, as has been found in the congenital bicuspid aortic valve.[7] There are several factors which determine the character of the murmur, the first of these being the size of the opening through which regurgitation is taking place. Clinical experience has shown that when free aortic regurgitation increases in severity there may be a reduction in the intensity of the murmur. The second factor is the difference in pressure on either side of the opening. From an analysis of the pressure curves obtained by Wiggers[8] in normal animals and in those with aortic regurgitation, it can be seen that the difference in pressure on either side of the aortic valve increases from the time of its closure until just after the time of opening of the auriculoventricular valves. The maximal difference of pressure is between 0.08 and 0.10 second after the closure of the semilunar valves, and this is followed by a slowly declining pressure difference. A third factor is probably the size of the cavity into which regurgitation is taking place. Finally, it may be that the turbulence produced by the closure of the semilunar valves is such as to keep even deformed cusps in temporary apposition and thus momentarily to delay the onset of regurgitation. The last three factors may help to explain the configuration of the murmurs illustrated in this paper.

AUSCULTATORY CHARACTERISTICS OF THE BASAL DIASTOLIC MURMUR

The usual descriptions of the murmur state that it either replaces or follows immediately the second heart sound. It may be either high or low pitched and usually is of a blowing character and diminuendo throughout its duration. Only one[9] of the widely used textbooks states that there may be some delay between the end of the second sound and the onset of the murmur. None of them mentions that the murmur may ever be other than decrescendo in character. However, we have found on careful auscultation that the murmur has sometimes an early crescendo phase before the longer decrescendo phase, and Dr. Paul D. White personally stated[10] that he has not infrequently heard basal diastolic murmurs of this character. Those workers who have described the phonocardiogram in patients with aortic or pulmonary regurgitation have not shown this pattern.[11,12] Nevertheless, we shall demonstrate that a crescendo-decrescendo configuration is found on tracings not only from those patients in whom this is noted on auscultation, but also quite frequently from patients in whom the murmur is heard as purely decrescendo in character.

PHONOCARDIOGRAPHIC TECHNIQUE

The technique of taking sound tracings is of considerable importance. The patient should be comfortable and warm, and in a quiet room free from nearby sources of interference from alternating current. The sound or murmur to be recorded should be carefully located and the point of maximal intensity determined. The stethoscopic microphone and audiophone are then used to confirm the similarity of the electrical reproduction to what was heard with the acoustic stethoscope, and a choice of chestpiece best suited to register the murmur is made.

The most useful chestpiece for the high-pitched type of diastolic murmur is the Bowles chestpiece with Bakelite diaphragm 0.015 inch thick and with a free working diameter of 1-3/8 inches. These are the diameter and thickness most commonly used in the commercial acoustic stethoscope. The Bowles chestpiece is used only with the logarithmic microphone. When the murmur is extremely high pitched and faint, a similar Bowles chestpiece with a Bakelite diaphragm of 0.035 inch thickness is occasionally more satisfactory.[3] However, in the majority of tracings taken in this study, we have used the open bell chestpiece with the logarithmic microphone. This combination is somewhat more satisfactory when the murmur to be reproduced is of moderate or low frequency.

The application of the chestpiece must be made with care so that it is perfectly sealed to the chest wall. When the cardiac impulse is forceful, or during certain phases of respiration, there may be temporary lifting of the chestpiece from the chest wall. This produces artefacts on the tracing of which the operator may not be aware at the time the tracing is taken, especially when proper correlation with the auscultatory findings has not been made. Fig. 1 shows a tracing in which such artefacts are present.

The position of the patient should be altered by means of an easily adjustable couch or bed until the jugular pulse in the neck is most clearly seen. The sound tracings are taken in this position, so that satisfactory jugular pulse tracings can be made at the same time. In an occasional case in which the murmur is audible only in some other position, further tracings can be taken subsequently in the desired position. All records are taken with the breath held in expiration.

The degree of amplification must be determined by experience. We have not considered it necessary to keep the upper parts of loud sounds and murmurs on the 6.0 cm. paper. With insufficient amplification the tracings must be studied by means of a magnifying glass and are unsuitable for analysis or reproduction.

We have recently standardized our phonocardiograms by means of a sound source of constant frequency and intensity, namely, 500 cycles a second at 80 decibels above the threshold of audibility. After each tracing is made and before the controls of the instrument are touched, the microphone is removed from the patient, the chestpiece is detached, and the standard sound is introduced. The width of the dark band at the end of the tracings therefore represents a

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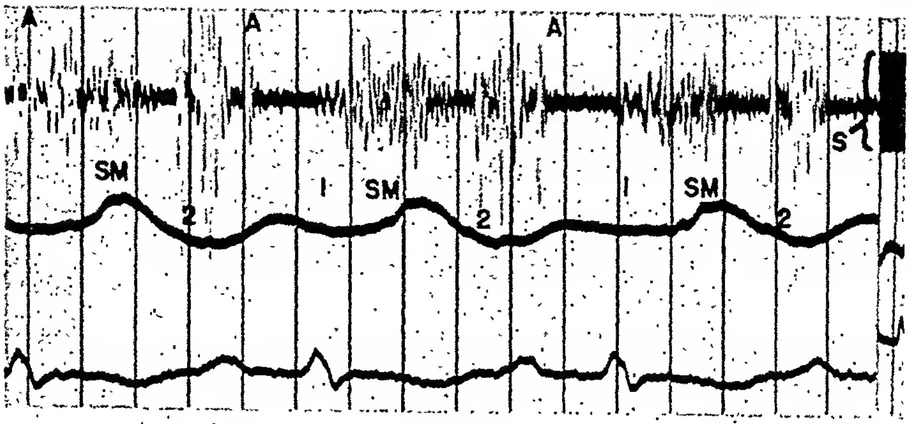

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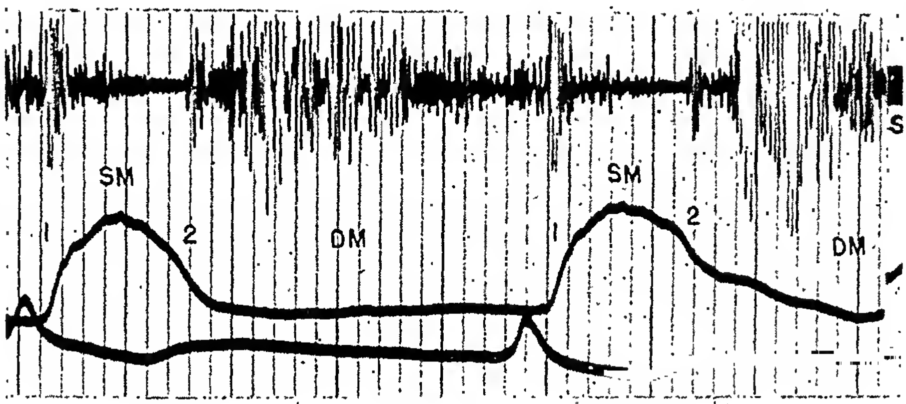

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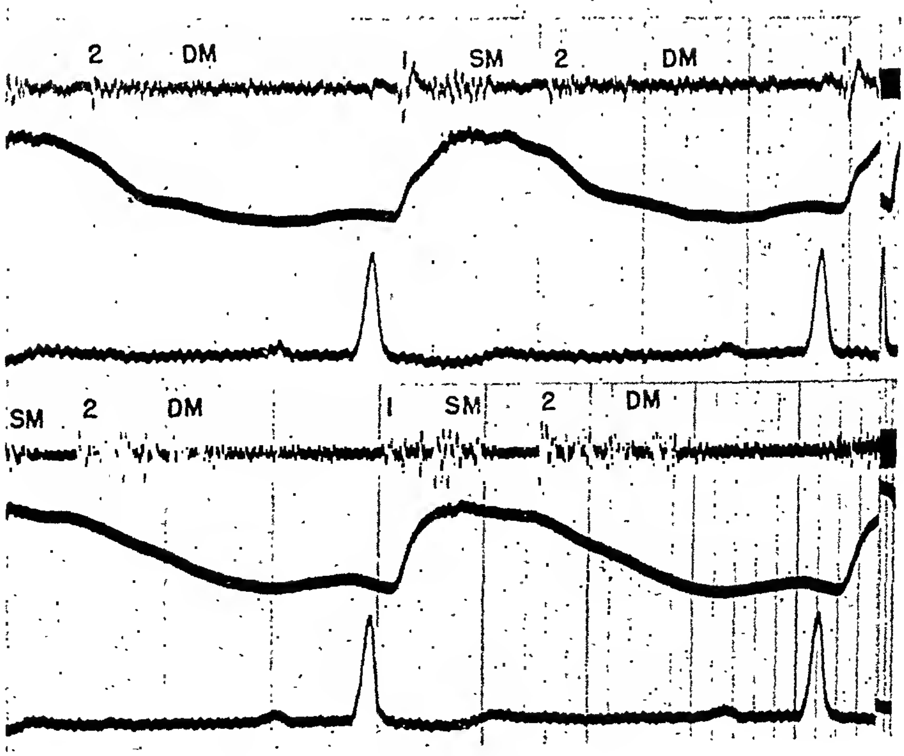

Figs. 1-3.—*See opposite page for legends.*

constant reference of sound intensity analogous to the one millivolt used in the standardization of the electrocardiogram. A full description of this standardization is the subject of a separate communication.[13]

All of our tracings have been taken at a paper speed of 75 mm. per second.

When carefully attentive to technique, we have never failed to record even the most faint diastolic murmur and have frequently demonstrated murmurs where auscultation had produced a difference of opinion as to their presence. In addition, there have been cases in which no diastolic murmur was ever heard but in which we have registered vibrations in early diastole. Tracings of these patients will be shown, and the reasons why such vibrations were not audible will be discussed.

LOUD BASAL DIASTOLIC MURMURS

The intensity of murmurs as they are heard on auscultation may be usefully expressed in the manner introduced by Levine.[14] A murmur is considered to be Grade 6 in intensity when it can be heard with the ear at some distance from the chest wall, while very loud, moderate, slight, and very slight murmurs are classified as Grade 5, Grade 4, Grade 3, Grade 2, and Grade 1, respectively. The loud (Grade 4) basal diastolic murmurs are very easily recorded, and it is in these murmurs that a crescendo-decrescendo configuration can most readily be demonstrated. The first tracing (Fig. 2) is taken from a patient in whom the character of the murmur on auscultation was such that it increased in intensity in early diastole, then gradually diminished in intensity up to the time of the subsequent first heart sound. The tracing shows that the maximal intensity of the murmur occurs between 0.10 and 0.20 second from the closure of the semilunar valves.

The patient whose tracing is shown in Fig. 3 had on auscultation a murmur of more usual character. It was loud and blowing and was thought to be purely decrescendo. The stethoscopic tracing demonstrates how poorly this microphone reproduces the murmur, while in contrast, the low frequency components of the first sound and the systolic murmur are well recorded. This is because

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Fig. 1.—Artefacts (*A*) caused by lack of proper sealing of the lip of the open bell to the chest wall. *Upper tracing:* stethoscopic microphone with medium open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

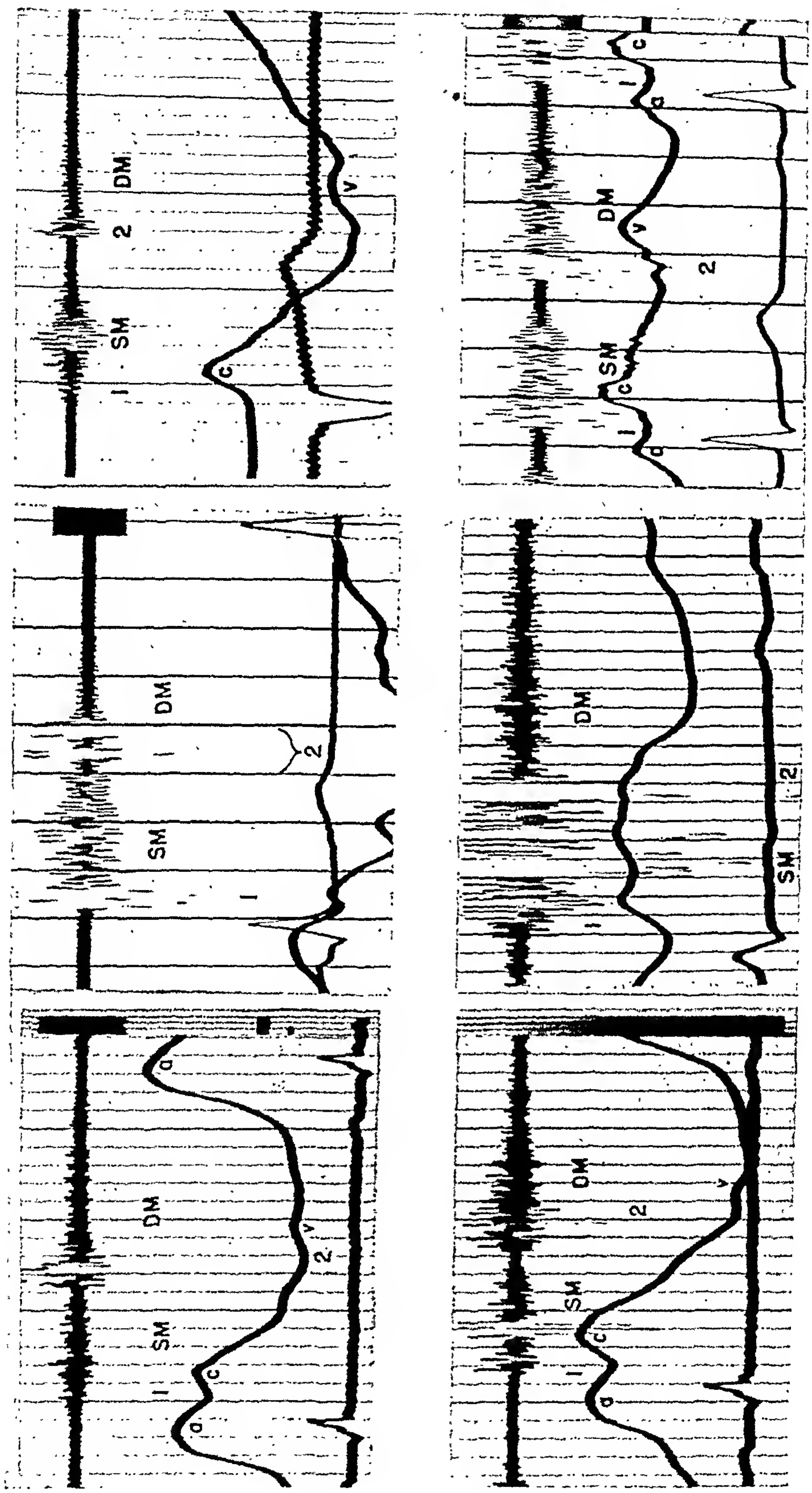
Note the standard sound *s* described in the text, which is used in subsequent illustrations.

Fig. 2.—Man, aged 46. Rheumatic heart disease following rheumatic fever at age 19. Mitral and aortic valvular disease.

Upper tracing: logarithmic microphone with large open bell over left sternal border in fifth intercostal space. *Central tracing:* jugular pulse. Because of free aortic regurgitation with marked arterial pulse in the neck, this tracing is almost wholly arterial. *Lower tracing:* electrocardiogram, Lead II.

Fig. 3.—Woman, aged 55. No history of rheumatic fever or syphilis. Admitted after sudden episode of shortness of breath during previous night. Diagnosis: syphilitic aortic insufficiency with Grade 4 aortic diastolic murmur.

Upper sound tracing: stethoscopic microphone with large open bell over the third left intercostal space. *Lower sound tracing:* logarithmic microphone with large open bell over the same area. *Reference tracing:* jugular pulse (mainly arterial because of the marked pulsation in the neck), and electrocardiogram, Lead I.



Figs. 4-8.—See opposite page for legends.

the diastolic murmur contains few and insignificant low frequency components. It is well reproduced on the logarithmic tracing and is seen to have a quite definite crescendo-decrescendo configuration. It is difficult to explain why this quality of the murmur was not audible, for the intensity of the second sound is hardly sufficient to produce a fatiguing effect on the hearing mechanism. The fact that the diastolic murmur persists throughout diastole and is not merely an unsteady base line is proved by the short interval of silence prior to the second heart sound.

MODERATE BASAL DIASTOLIC MURMURS

The phonocardiograms of Grade 3 basal diastolic murmurs may show the purely decrescendo configuration which is the usual auscultatory character of these murmurs. Such tracings are shown in Figs. 4,*A* and 4,*B*, which also demonstrate the advantages of using the Bowles chestpiece. These tracings show how the Bowles chestpiece attenuates the first and second sounds and the systolic murmur, allowing a considerable increase in amplification, which enables better registration of the diastolic murmur. It is evident from both tracings that the murmur starts with the second heart sound and has a purely decrescendo configuration.

Duplication of the second sound at the base is usually attributed to asynchronous closure of the semilunar valves. If a diastolic murmur is present in such cases, phonocardiograms will show that the murmur follows either the first or second part of the split sound. However, as we shall demonstrate later, when the second sound is not duplicated there may be an interval of silence before the onset of the diastolic murmur. This fact, together with the frequent occurrence of a crescendo-decrescendo configuration of the murmur, would make

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Fig. 4.—Man, aged 43. No history of rheumatic fever or syphilis: Gradual shortness of breath for three months, ankle edema, and precordial pain on exertion. Grade 3 blowing diastolic murmur heard along left sternal border.

A, Logarithmic microphone with large open bell over second left intercostal space.

B, Logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) at same location using greater amplification. Note that in *B* the band inscribed by the standard sound extends below the base line of the electrocardiogram.

Reference tracings: jugular pulse and electrocardiogram, Lead I.

Fig. 5.—Boy, aged 9. Rheumatic heart disease following rheumatic carditis at age 5. Grade 3 blowing diastolic murmur heard along left sternal border.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

Fig. 6.—Man, aged 56. Repeated attacks of rheumatic fever at ages 8, 16, 26, and 40. Rheumatic heart disease found since last of these attacks. Congestive failure during last year. Grade 4 systolic and Grade 3 diastolic murmurs in second left intercostal space.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 7.—Man, aged 76. No history of rheumatic fever. Indefinite history of syphilis at age 30. Increasing exertional dyspnea for last two years with recent ankle edema. Heart greatly enlarged with Grade 3 diastolic murmur at second left intercostal space. Auricular fibrillation.

Upper tracing: logarithmic microphone with large open bell at second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

Fig. 8.—Boy, aged 6. Rheumatic heart disease with mitral and aortic involvement following rheumatic fever at age 4. Grade 2 systolic murmur masking first sound, and Grade 3 blowing diastolic murmur at second left intercostal space.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

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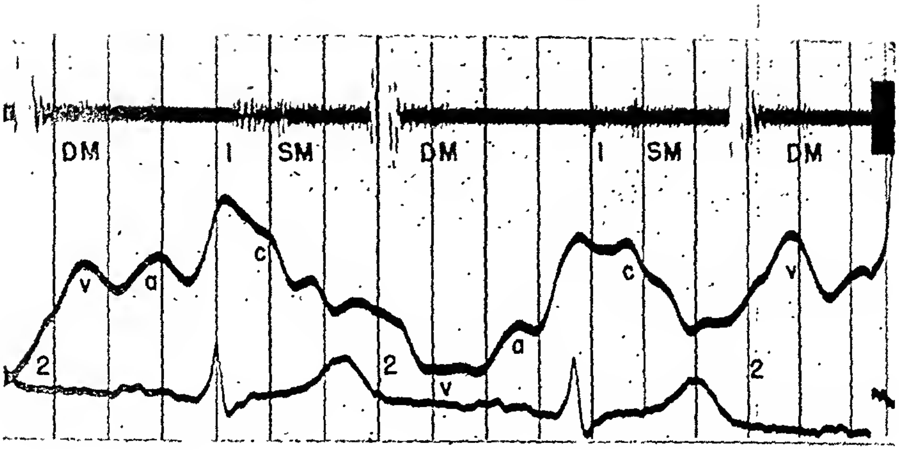

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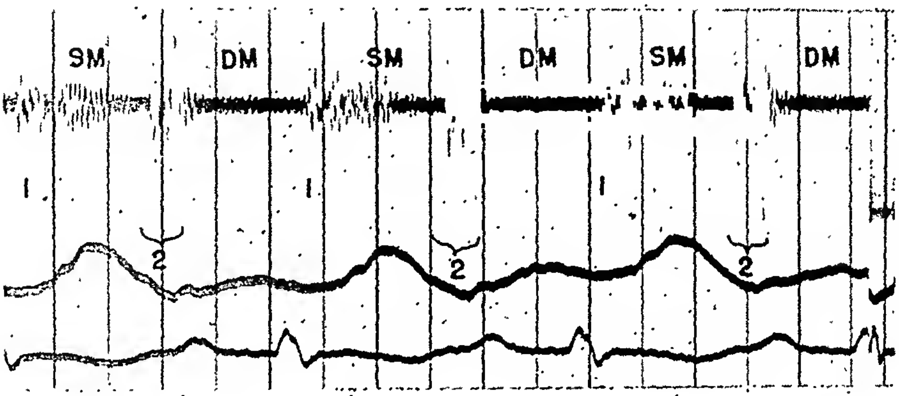

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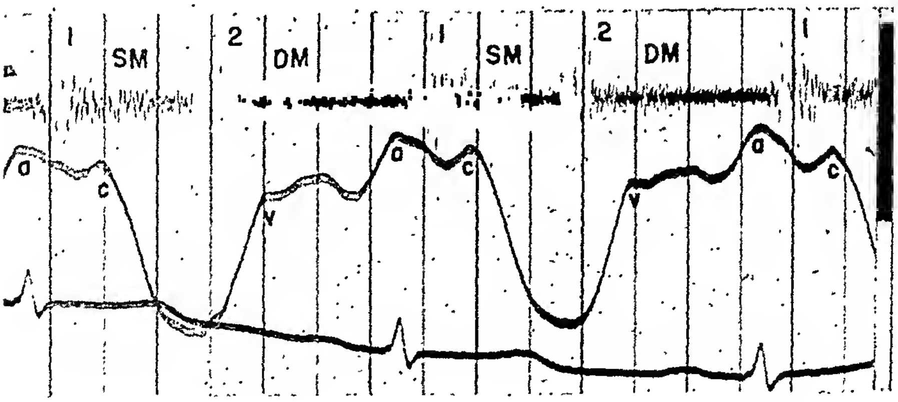

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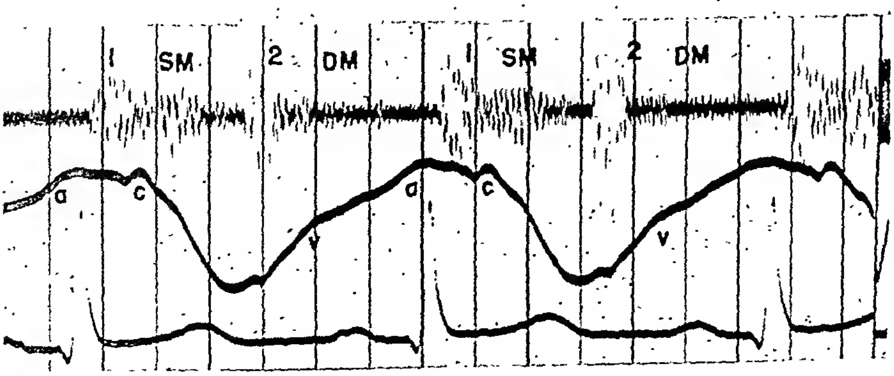

Figs. 9-12.—*See opposite page for legends.*

it unjustifiable to assume that the diastolic murmur was necessarily related to that part of the duplicated sound which immediately preceded it. The phonocardiogram of a moderate diastolic murmur following a duplicated second sound is shown in Fig. 5. This tracing presents a moderately coarse murmur starting with the latter part of a duplicated second sound and continuing in a decrescendo manner into diastole. Since there are a few vibrations between the components of the duplicated second sound, the murmur may be a crescendo-decrescendo murmur following the first component of the split sound. However, it is more probable that the murmur is related to the second part of the split sound.

The crescendo-decrescendo configuration found in loud diastolic murmurs is also found in phonocardiograms of moderate murmurs. Moderate basal diastolic murmurs in rheumatic and syphilitic aortic insufficiency showing this configuration are presented in Figs. 6, 7, and 8. The diastolic murmurs in these three tracings are somewhat similar, all being crescendo-decrescendo in configuration and of moderate frequency. The systolic murmurs in Figs. 7 and 8 end in early systole and thus provide a steady base line prior to the second heart sound, in contrast to which the diastolic murmurs stand out well.

SLIGHT BASAL DIASTOLIC MURMURS

On auscultation there may be some variation in character of the slight (Grade 2) basal diastolic murmur. This murmur is usually described as high-pitched and blowing but is occasionally coarse and low in pitch. Phonocardiograms of such murmurs show a greater degree of variation in frequency, configuration, and duration. Murmurs of moderately high frequency are shown in Figs. 9 and 10. In both of these tracings the vibrations constituting the murmur are low in amplitude. Their presence can be readily confirmed by contrasting the second half of diastole with the first. In addition, there is in Fig. 10 an interval of comparative silence between the systolic murmur and the second heart sound. The moderately high frequency vibrations which make up the

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Fig. 9.—Boy, aged 13. Rheumatic heart disease following acute rheumatism two years previously. Mitral and aortic insufficiency; congestive failure. Grade 2 blowing diastolic murmur along left sternal border.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 10. Girl, aged 16. Rheumatic heart disease since rheumatic fever at age 8. Possible additional patent auricular septum. Grade 2 blowing diastolic murmur along left sternal border. Grade 2 to 3 systolic murmur at pulmonary base with accentuated and duplicated second sound.

Upper tracing: logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 11.—Boy, aged 14. Rheumatic heart disease following probable rheumatic fever at age 4, with recurrence at age 11. Grade 2 aortic diastolic murmur along left sternal border. Blood pressure 105/65.

Upper tracing: logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) over fourth left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 12.—Boy, aged 14. Rheumatic heart disease following rheumatic fever at age 8. Recurrences three years and again one month before tracing. Grade 2 blowing diastolic murmur along left sternal border.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

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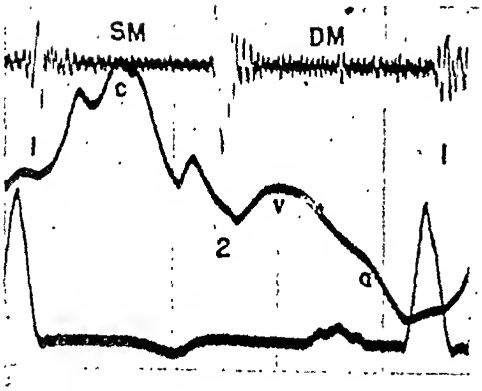

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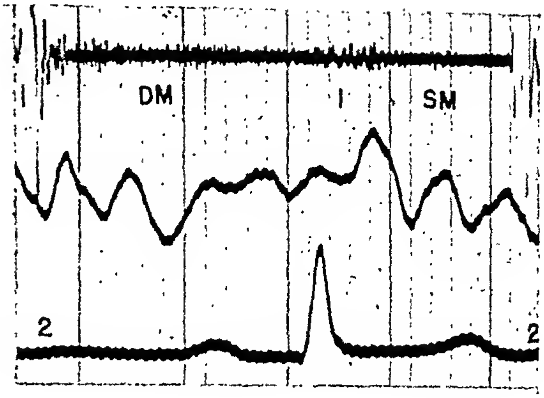

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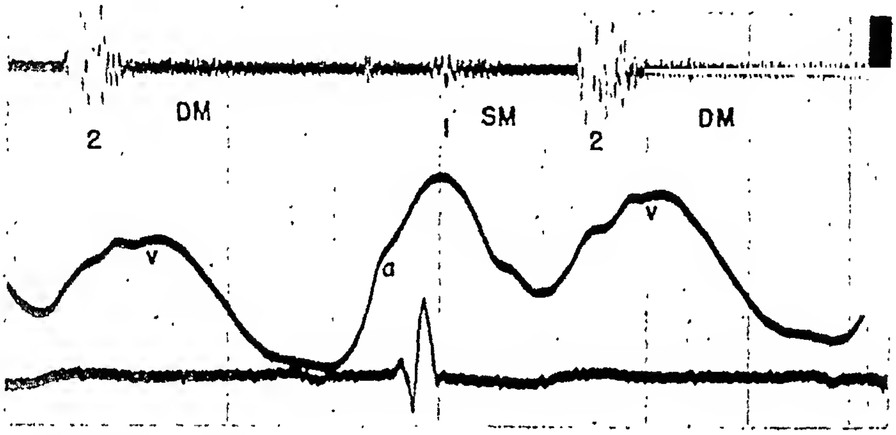

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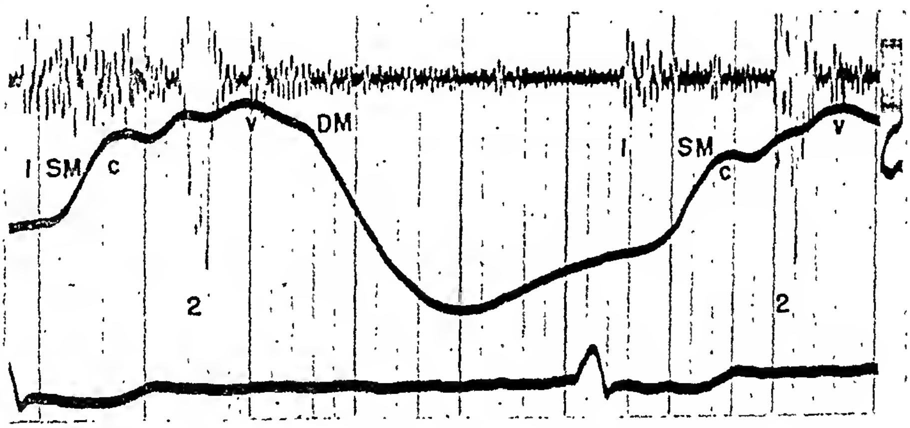

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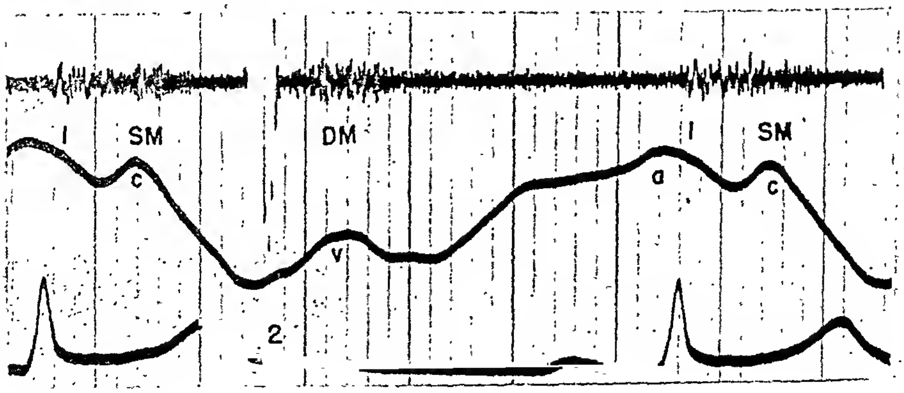

Figs. 13-17.—*See opposite page for legends.*

diastolic murmur are seen to start not immediately with the second sound but after a short period of lower frequency vibrations. This may be explained by delay in the onset of regurgitation, due to momentary complete apposition of the valve cusps, following the turbulence set up by their closure.

Slight murmurs not noticeably different on auscultation from the murmurs in the two previous cases are shown in Figs. 11 and 12, although it is apparent from these phonocardiograms that the murmurs are composed of vibrations of somewhat lower frequency. The presence of a diastolic murmur in these tracings is decided by the greater amplitude of the vibrations in early diastole, in contrast to less intense vibrations both in late diastole and in late systole. The diastolic murmur in both cases has a crescendo-decrescendo configuration which varies somewhat with each cardiac cycle. In Fig. 13 the diastolic murmur is of moderately low frequency. It starts a short interval after the second heart sound and is then continuous throughout diastole. It can be contrasted with the systolic vibrations which are lower in intensity, especially just before the second sound. No systolic murmur was heard on auscultation. The diastolic murmur was blowing in quality and not unusual in character.

Although it is usual for the basal diastolic murmur to become minimal toward the end of diastole, this is not necessarily so, even in the slight (Grade 2) murmur. Figs. 14 and 15 show murmurs which continue throughout diastole without much diminution in intensity. In both of these tracings the diastolic murmur continues up to the time of the first heart sound and may be contrasted with vibrations of lesser intensity in the latter part of systole. In neither of these tracings is the decrescendo nature of the murmur at all marked.

The phonocardiogram of a patient with pulmonary regurgitation which shows a very different configuration is seen in Fig. 16. This tracing is of in-

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Fig. 13.—Man, aged 23. Rheumatic heart disease following acute rheumatism complicating scarlet fever at age 12. Heart considerably enlarged with Grade 2 diastolic murmur along left sternal border.

Upper tracing: logarithmic microphone with large open bell over third left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 14.—Woman, aged 22. Rheumatic heart disease following attacks of rheumatic fever at ages 9, 11, and 12. Minimal cardiac enlargement with Grade 2 aortic diastolic murmur along left sternal border. No diastolic murmur at apex.

Upper tracing: logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) over fourth left intercostal space after exercise. *Central tracing:* linear phonocardiogram at apex. *Lower tracing:* electrocardiogram, Lead II.

Fig. 15.—Man, aged 74. Syphilis at age 35. Recent congestive failure with some hypertension. Grade 2 blowing early diastolic murmur in third left intercostal space following accentuated second sound. Rumbling diastolic murmur just medial to apex. Fluoroscopy revealed hilar dance without increase in aortic pulsation. Blood pressure 160/85. Diastolic murmur probably due to pulmonary regurgitation.

Upper tracing: logarithmic microphone with large open bell over fourth left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

Fig. 16.—Man, aged 28. Rheumatic heart disease without known rheumatic fever or chorea. Mitral and probably tricuspid stenosis; auricular fibrillation; congestive failure. Variable low-pitched Grade 2 blowing diastolic murmur localized to second left intercostal space, attributed to pulmonary regurgitation.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

Fig. 17.—Boy, aged 15. Rheumatic heart disease following rheumatic fever at age 11. Heart border line in size. Grade 2 blowing diastolic murmur along left sternal border and quite widely conducted. No mitral diastolic murmur.

Upper tracing: logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) at second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

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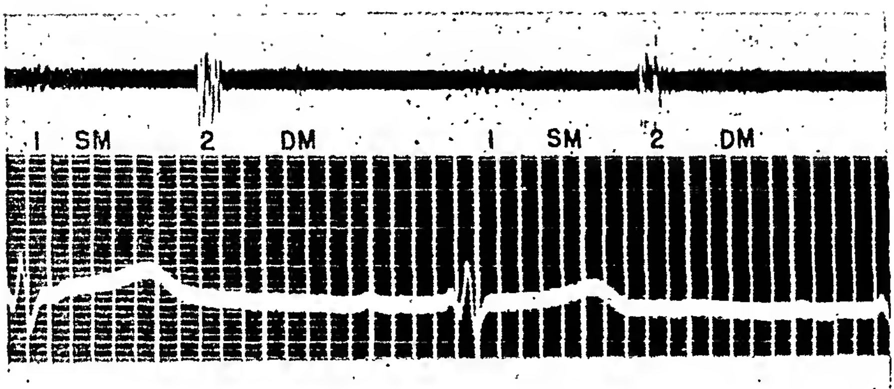

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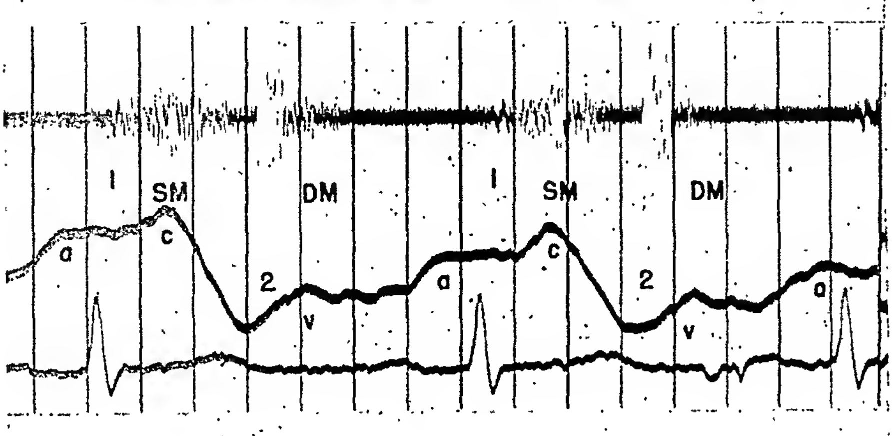

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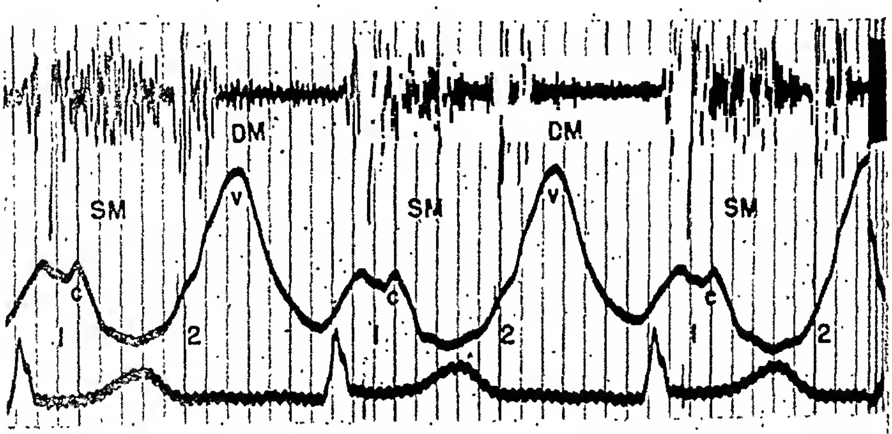

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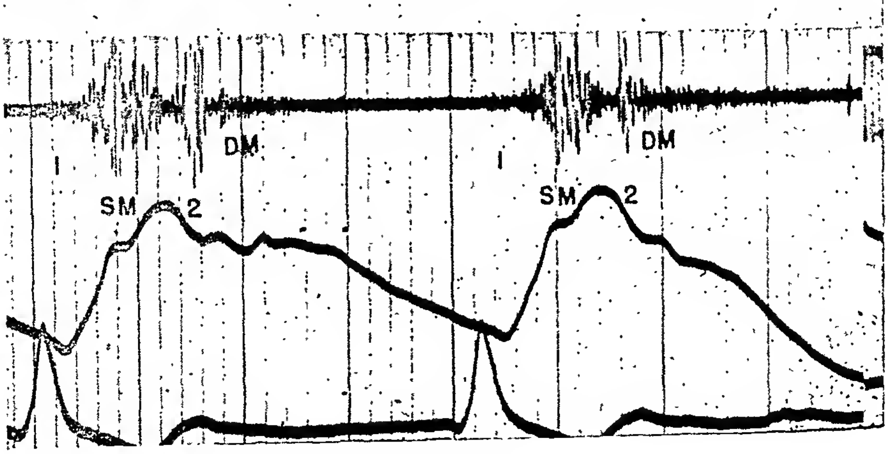

Figs. 18-21.—*See opposite page for legends.*

terest in that the diastolic murmur, which is of decrescendo type, appears to follow the latter part of a widely split second sound. By reference to the apex cardiogram it was found that the A-V opening occurred before the second part of the split sound was inscribed. This part of the sound is therefore probably not an opening snap and can be attributed to a delayed closure of the aortic valve following an earlier and accentuated sound of pulmonary valve closure. If this hypothesis is correct and if the diastolic murmur is due to pulmonary regurgitation, then it must be fortuitous that the murmur appears to originate with the latter part of the duplicated second sound. In other words, the latter sound must be inscribed on the beginning of a diastolic murmur of delayed onset, with, perhaps, a crescendo-decrescendo configuration.

Phonocardiograms of slight basal diastolic murmurs will occasionally show the conspicuous crescendo-decrescendo configuration seen with louder murmurs. Such a tracing is shown in Fig. 17, which is taken from a patient in whom the diastolic murmur was not noted on auscultation to be of unusual character. However, there is a progressive increase in the intensity of the murmur up to about the time of the apex of the V wave in the phlebogram, when it is followed by a fairly marked reduction in intensisty.

VERY SLIGHT BASAL DIASTOLIC MURMURS

The very slight murmur of aortic or pulmonary regurgitation is the murmur which has hitherto proved the most difficult to register. Especially has this been so when the murmur was not only extremely faint but also very high in pitch. Such circumstances existed at the time of the tracing shown in Fig. 18. In this patient the murmur was barely audible with the use of an acoustic stethoscope and a Bowles chestpiece of usual thickness (0.015 inch). It was considerably more pronounced when heard through the audiophones with the phonocardiograph amplifier and the Bowles chestpiece with a thick diaphragm (0.035 inch). This illustrates the circumstances in which the Bowles chestpiece

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Fig. 18.—Man of middle age with syphilitic aortitis and dextrocardia. Grade 1 high-pitched diastolic murmur only just above threshold of audibility.

Upper tracing: logarithmic microphone with Bowles chestpiece with thick diaphragm (0.035 inch) over area of maximal intensity. *Lower tracing:* electrocardiogram, Lead II.

Fig. 19. Girl, aged 14. Rheumatic heart disease following rheumatic fever three years and again five months previously. Grade 2 systolic and Grade 1 blowing diastolic murmurs heard in third left intercostal space.

Upper tracing: logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) over third left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 20.—Girl, aged 10. Pains in legs at age 4, when moderate systolic murmur over left sternal border was found. Slight cardiac enlargement at time of tracing with Grade 3 systolic and Grade 1 diastolic murmurs at second left intercostal space. Probably congenital rather than rheumatic heart disease.

Upper tracing: logarithmic microphone with large open bell over fourth left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 21.—Man, aged 50. No history of rheumatic fever. Known hypertension for five months; recent congestive failure. Grade 4 systolic murmur with thrill over aortic area, and Grade 1 diastolic murmur. Because of definite rumbling apical diastolic murmur, rheumatic as well as hypertensive heart disease was diagnosed.

Upper tracing: logarithmic microphone with large open bell at second left intercostal space. *Central tracing:* jugular pulse. Tracing mostly carotid because of marked arterial pulsation in neck. *Lower tracing:* electrocardiogram, Lead I.

with a thick diaphragm when used in conjunction with an electronic amplifier is of definite value. It should be emphasized that this is of no value in the acoustic stethoscope, as amplification is essential when a diaphragm of such thickness is used. The murmur is seen to start a short interval after the second sound and is of rather high frequency and crescendo-decrescendo in configuration. The second sound in this patient was of considerable intensity and would therefore produce a fatiguing effect on the hearing mechanism, which, persisting for a short period in diastole, would tend to mask the murmur.

The tracing of a second patient with a very slight basal diastolic murmur is shown in Fig. 19. In this case the murmur was satisfactorily registered by use of the Bowles chestpiece with a thin diaphragm. The murmur is crescendo-decrescendo in configuration, being maximal shortly after an accentuated second sound, at about the time of the apex of the V wave in the jugular phlebogram. It is of moderate frequency, being lower in frequency than the murmur in Fig. 18.

The relationship of a very slight murmur to a duplicated second sound is illustrated by Figs. 20 and 21. The first of these tracings (Fig. 20) shows a duplicated second sound and a crescendo-decrescendo diastolic murmur, with maximal intensity at the apex of the V wave of the phlebogram. The systolic murmur usually terminates just prior to the second sound. The second tracing (Fig. 21) demonstrates that the onset of the diastolic murmur may in some cycles be separated from the second sound by a short, silent interval. If there had been duplication of the second sound in this case, and if the murmur had been related to the first part of the split sound, then it might have appeared sometimes to start only with the second component. It should be noted that the diastolic murmur is well recorded in this tracing, although it was very slight on auscultation. This is probably explained by the considerable intensity of the systolic murmur and second sound, which would cause fatigue of the hearing mechanism for a short period in early diastole when the diastolic murmur is most intense.

DIASTOLIC MURMURS WHICH ARE QUESTIONABLE ON AUSCULTATION

In the four patients with very slight basal diastolic murmurs whose tracings are illustrated, there was in each case a difference of opinion as to whether the murmur was present or not. Some observers had in every instance failed to hear the murmurs. Even greater uncertainty was expressed in the case of the patient whose tracing is shown in Fig. 22. In this tracing the fourth component of the second sound, the A-V opening sound, can be clearly seen. Between this sound and the third sound there is a regular series of moderately fine vibrations which constitute a diastolic murmur. The reason this diastolic murmur was not heard with certainty on auscultation is that the great intensity of the systolic murmur and the second component of the second sound would cause a fatiguing effect on the hearing mechanism during early diastole.

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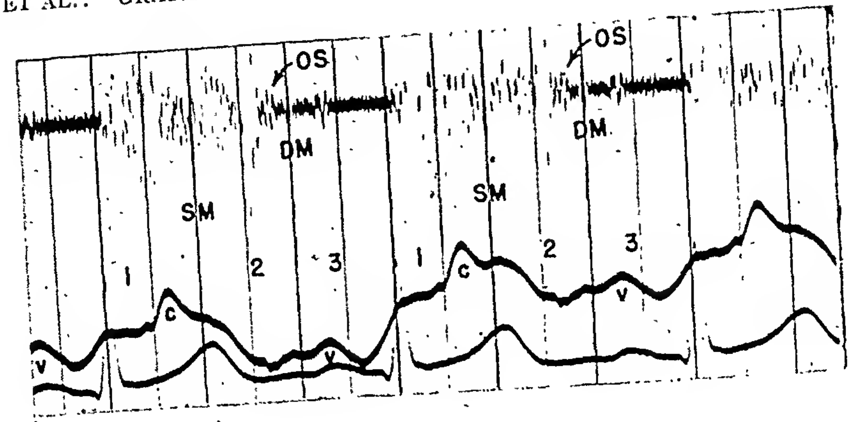

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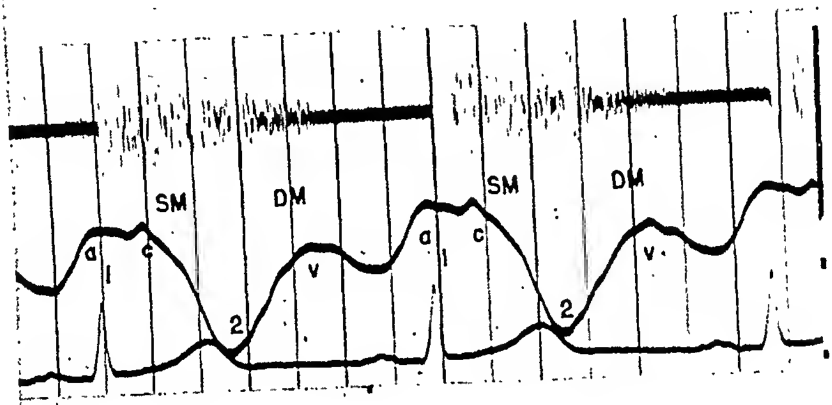

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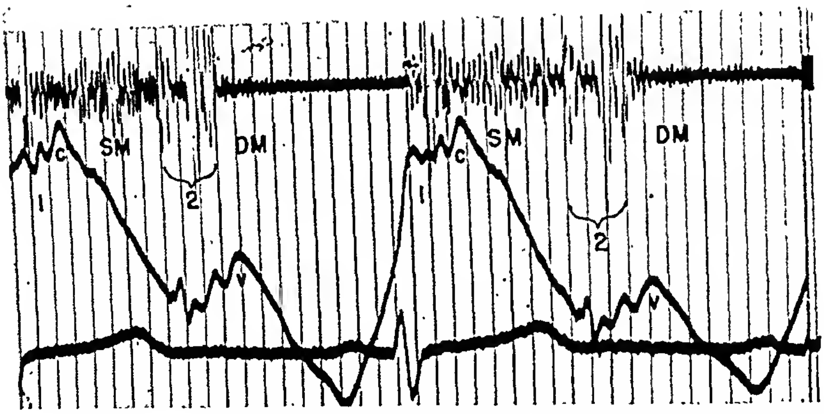

Fig. 22.—Girl, aged 15. Rheumatic heart disease following recurrent attacks of rheumatic fever during last two years. Grade 3 systolic murmur at fourth left intercostal space with questionable, very slight diastolic murmur.

Upper tracing: logarithmic microphone with large open bell at fourth left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 23.—Girl, aged 7. Acute rheumatic fever following febrile cold two months previously. Grade 3 systolic murmur at third left intercostal space with scratchy murmur in diastole which was thought by some observers to be friction rub, and by others rather harsh murmur of aortic regurgitation.

Upper tracing: logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) over third left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 24.—Boy, aged 15. No history of rheumatic fever. Moderate rachitic deformity of chest; heart normal in size. Grade 3 systolic murmur and accentuated second sound at second left intercostal space. No diastolic murmur heard. Murmur considered probably physiological.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

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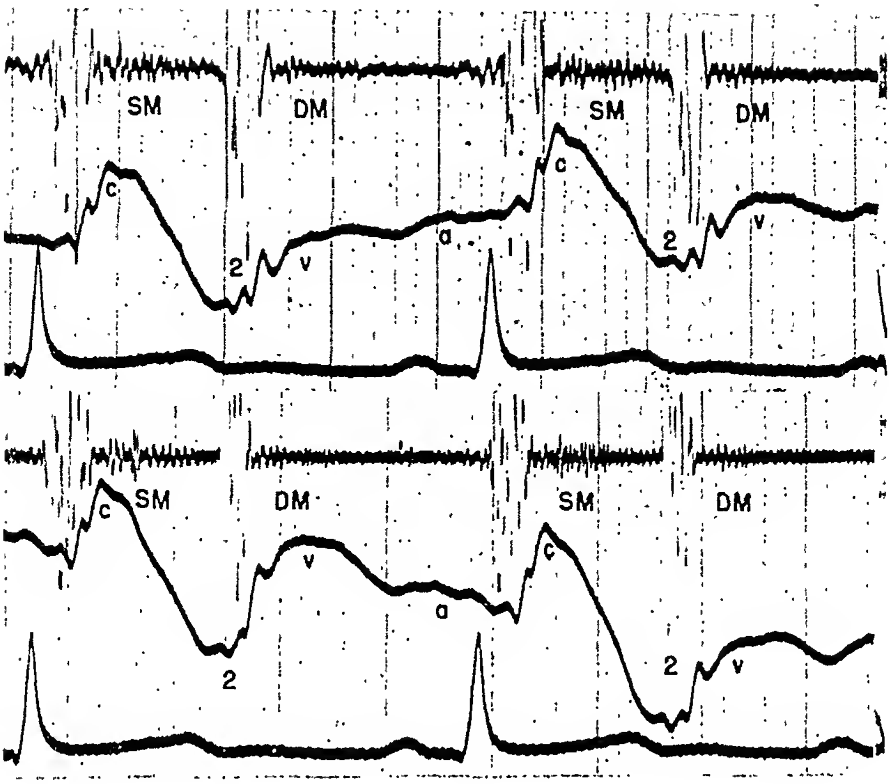

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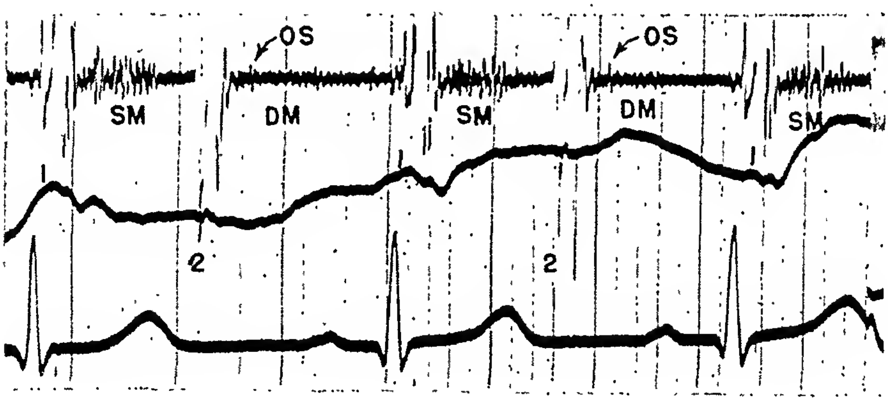

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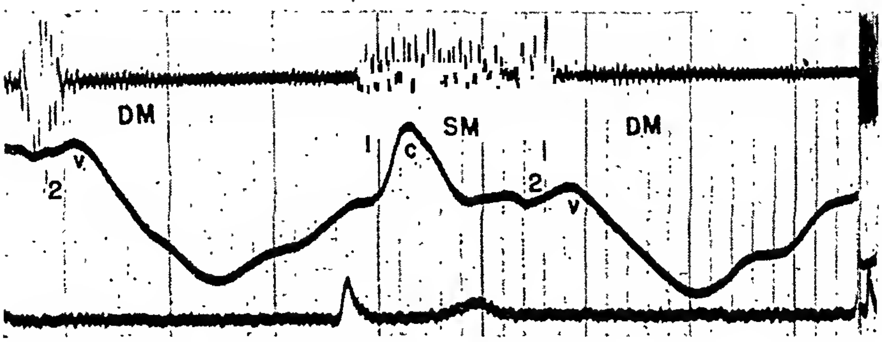

Figs. 25-27.—*See opposite page for legends.*

DIFFERENTIAL DIAGNOSIS FROM PERICARDIAL FRICTION RUB

It is usually quite simple to differentiate a friction rub from the diastolic murmur of aortic regurgitation. In doubtful cases the phonocardiogram may be of some help, since it provides evidence that can be analyzed more carefully than the sounds heard on auscultation. The phonocardiogram in Fig. 23 is of a patient in whom a rather scratchy diastolic sound was heard, and there was some question as to whether aortic regurgitation was present. The diastolic murmur is very clearly demonstrated by the tracing. Its onset is separated from the second sound by a short period of silence and corresponds to the time of opening of the A-V valves. The murmur is of moderate frequency and diminuendo configuration. These characteristics are frequently found in the murmur of aortic regurgitation; they would favor an interpretation on this basis rather than that of pericardial friction rub.

BASAL DIASTOLIC VIBRATIONS WHERE NO MURMUR WAS AUDIBLE ON AUSCULTATION

The following six phonocardiograms were found among tracings on 200 patients in whom further study of auscultatory findings was thought to be desirable. They were the only tracings in which diastolic vibrations considered to be of significance were located at the base of the heart in the absence of any audible murmur. Vibrations of significance are those which recur regularly in each cardiac cycle, to which they have a definite relation manifested by a period of maximal or minimal intensity. Other variations in the base line may be due to noises in the room where the phonocardiograms are recorded, or they may be produced by involuntary muscular movements of the chest wall; these base-line variations will be unrelated to the cardiac cycle. The tracings in Figs. 24 25 were made from patients in whom no diastolic murmur was heard at apex or base.

The tracing in Fig. 24 shows that the second sound is in actual fact widely split. The first element of the sound was not identified clinically, probably because it is continuous with the systolic murmur. In diastole there are vibrations of decrescendo configuration and moderately low frequency continuing almost to the first sound. The reason no diastolic murmur was heard is partly that the vibrations are of comparatively low frequency, occurring in a region of the auscultatory spectrum in which acuity of hearing is reduced. In addition,

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Fig. 25.—Girl, aged 14. Rheumatic fever at age 4. Gradual development of Grade 2 apical systolic murmur during last seven years. No diastolic murmur heard. X-ray films show enlargement of left auricle.

Upper sound tracing: stethoscopic microphone with large open bell over second left intercostal space. *Lower sound tracing:* logarithmic microphone with large open bell over same area. *Reference tracing:* jugular pulse, and electrocardiogram, Lead II.

Fig. 26.—Boy, aged 4. Recent purpura accompanied by joint pains. Grade 2 to 3 apical systolic murmur and questionable apical diastolic murmur. No basal diastolic murmur was heard.

Upper tracing: logarithmic microphone with large open bell at second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 27.—Woman, aged 62. Arteriosclerotic heart disease; auricular fibrillation; moderate anemia; congestive heart failure. Rather rough systolic murmur at base, but no diastolic. Questionable apical diastolic murmur.

Upper tracing: logarithmic microphone with large open bell over second right intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

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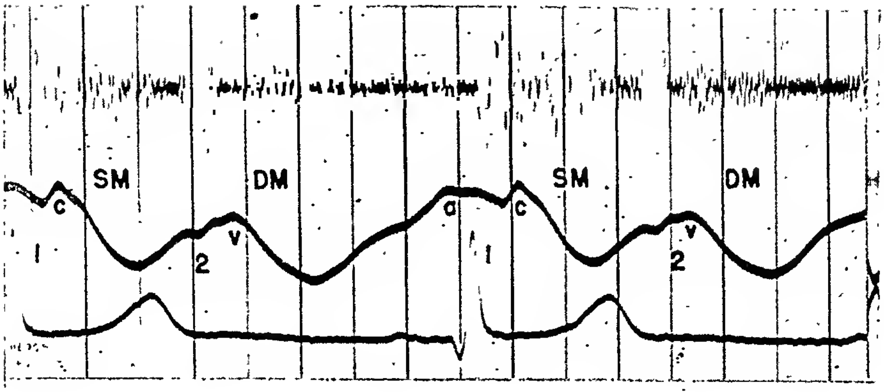

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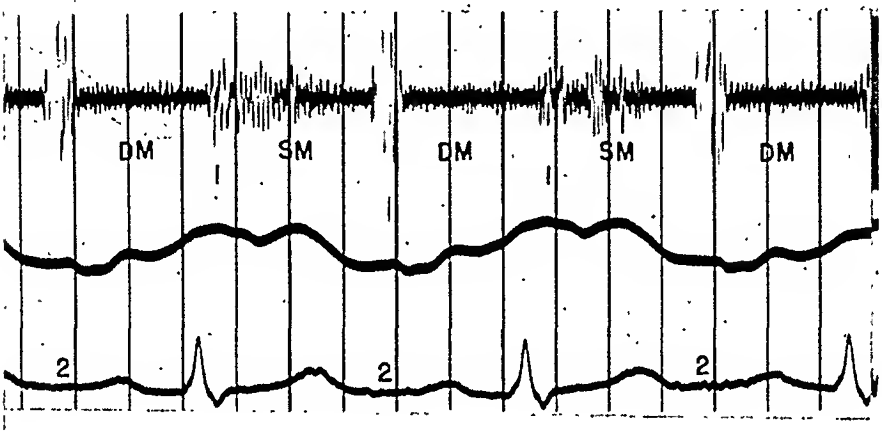

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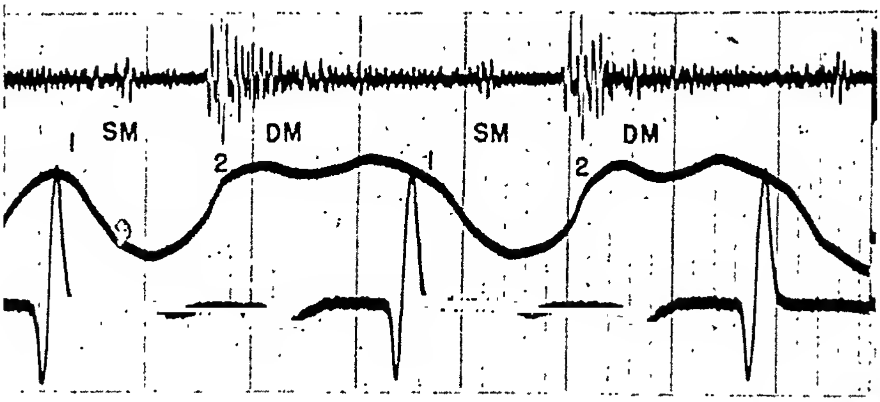

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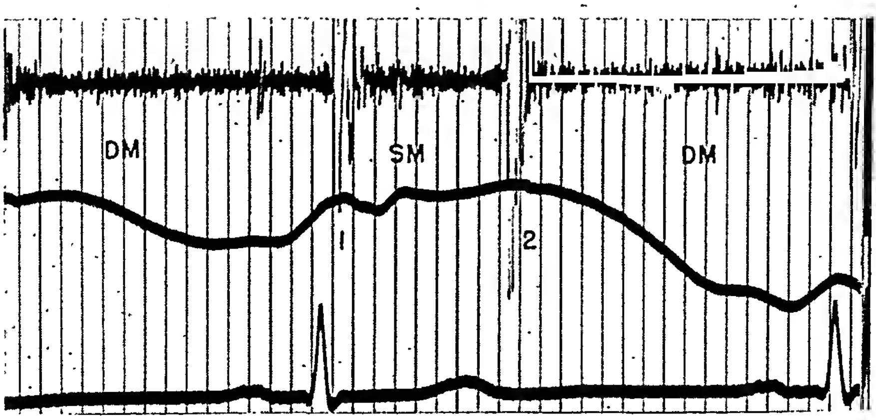

Figs. 28-31.—*See opposite page for legends.*

the loud systolic murmur and accentuated second sound would together exert a considerable fatiguing effect on the hearing mechanism which would persist through early diastole. Because of the moderate intensity and decrescendo configuration of the vibrations, they should probably be considered of a significance similar to that of an audible diastolic murmur. In this patient they would, therefore, suggest pulmonary insufficiency.

The tracings of Fig. 25 show vibrations starting in early diastole and becoming minimal prior to the auricular vibrations. They are of rather low frequency and are seen both in the stethoscopic and logarithmic recordings. The reason that no murmur was audible is probably the combination of low frequency with the masking effect of a loud second sound. Vibrations of this character have not been found in phonocardiograms of normal persons, but further experience must be obtained before they can be related to anatomical or physiological abnormalities of the heart.

Phonocardiograms of three patients were taken because question of an apical diastolic murmur had been raised. In all of these an apical diastolic murmur was recorded, but there were definite diastolic vibrations of different character at the base of the heart. The records are shown in Figs. 26, 27, and 28. The tracing in Fig. 26 shows definite vibrations at the time of the opening of the A-V valves. During early diastole there are vibrations of low intensity which can be contrasted with the comparatively steady base line at the very end of systole. The vibrations have no other characteristic configuration and their significance is unknown. In the phonocardiogram in Fig. 27 there are distinct vibrations of rather low frequency and intensity which are maximal in early diastole. At this period of the cardiac cycle there would probably be on auscultation some fatiguing of the hearing mechanism following the long, harsh systolic murmur and moderate second sound. This would explain why no murmur was audible. However, we must have further experience before we may interpret such vibrations as definitely indicative of valvular insufficiency. In Fig. 28 there is a short period of quiet at the end of systole in contrast to

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Fig. 28.—Girl, aged 8. Probable rheumatic heart disease since rheumatic fever one year previously. Grade 2 apical systolic with questionable apical diastolic murmur. No basal diastolic murmur.

Upper tracing: logarithmic microphone with large open bell at second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 29.—Girl, aged 10. Rheumatic heart disease following chorea at age 8 and rheumatic fever at age 9. Diastolic and presystolic murmurs heard at apex but no diastolic murmur at base.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 30.—Woman, aged 27. Short of breath since childhood. Progressive cyanosis, clubbing of fingers, and markedly increasing dyspnea during previous twelve months. Grade 3 diastolic murmur of unusual rumbling quality localized to third left intercostal space following markedly accentuated second sound.

Upper tracing: logarithmic microphone with large open bell at third left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I (upside down because of misplaced lead wires).

Fig. 31.—Woman, aged 24. No known rheumatic fever or heart disease. Diastolic murmur over lower central sternum, of rather coarse, blowing character, heard first during pregnancy. Following delivery murmur was less intense and rather more continuous in nature. Blood pressure, 110/70. No abnormality of heart on fluroscopy. Murmur was considered to be a mediastinal hum.

Upper tracing: logarithmic microphone with large open bell in third left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

which the diastolic vibrations are particularly apparent. They are crescendo-decrescendo in configuration, being maximal shortly after the apex of the V wave of the jugular phlebogram, and they continue throughout diastole. It is more difficult in this case than in the preceding to explain why no murmur was audible, though once again it is probable that the intensity of the systolic murmur and second sound exerted some fatiguing effect on the hearing mechanism. The moderate intensity and characteristic configuration of the vibrations in this patient would suggest aortic or pulmonary insufficiency.

Fig. 29 shows throughout diastole vibrations of moderate frequency and greater intensity than those in the quiet interval just preceding the second sound. The vibrations differ in configuration from those recorded at the apex where there was a period of quiet before the A-V opening and definite presystolic accentuation. The absence of a basal murmur on auscultation may have been due to the fatiguing effect of a rather loud second sound.

DIASTOLIC MURMURS OF UNUSUAL CHARACTER

An unusually coarse decrescendo diastolic murmur of moderately high intensity is present in Fig. 30. The murmur persists throughout diastole and can be contrasted with the comparative silence of the latter half of systole. The patient died a few months after the phonocardiogram was taken. It was expected that on post-mortem examination some form of congenital heart disease might be found, but there was no congenital defect. Marked right-sided hypertrophy secondary to pulmonary endarteritis was present, and the pulmonary artery was dilated and atheromatous. The diastolic murmur in this patient must be explained on the basis of pulmonary insufficiency due to pulmonary hypertension and dilatation of the pulmonary artery.

In Fig. 31 there is a decrescendo diastolic murmur coming off the second sound, followed by a gradual crescendo murmur through the remainder of diastole. The latter part is consistent with a mediastinal hum, but the early decrescendo phase would suggest the additional diagnosis of aortic or pulmonary regurgitation. However, the clinical features of this case make such a decision difficult.

THE DIASTOLIC MURMUR OF RETROVERTED AORTIC CUSP

The loud musical murmur of retroversion of one or more cusps of the aortic valve has long been recognized. Bellet and others,[15] who published a phonocardiogram of one of these cases, have discussed the mechanism of its causation. One patient under our observation was found to have a very loud diastolic murmur of characteristic quality which later disappeared, leaving only a moderate murmur of aortic insufficiency. Tracings before and after the disappearance of the murmur are shown in Fig. 32. The marked and rapid change in this murmur gives strong support to the theory that the murmur is due to retroversion of an aortic valve cusp. In this case the retroverted cusp apparently underwent spontaneous return to its normal position, leaving some evidence of underlying aortic valve disease with aortic insufficiency.

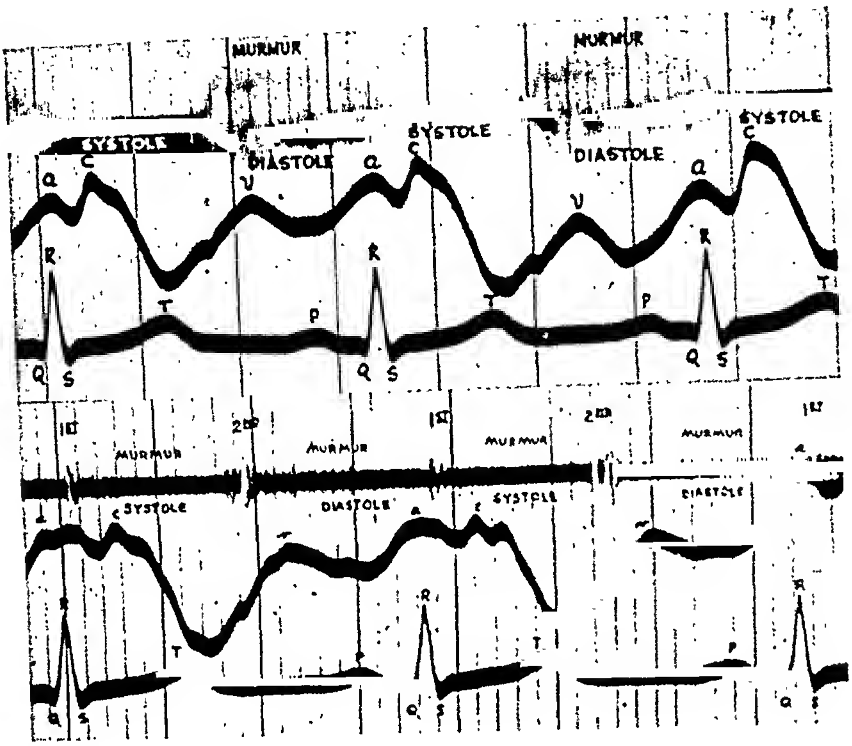

Fig. 32.—Boy, aged 16. After nine days of acute rheumatic fever suddenly developed Grade 6 diastolic murmur in aortic area, of "seagull" type with thrill. This lasted fourteen weeks and suddenly decreased to Grade 3 without thrill.

Upper sound tracing: logarithmic microphone with large open bell over aortic area. *Lower sound tracing:* logarithmic microphone with Bowles chestpiece (0.015 inch diaphragm) over same area some weeks later, when murmur had undergone sudden decrease in intensity. *Reference tracings:* jugular pulse and electrocardiogram, Lead I.

The musical quality and great intensity of the diastolic murmur shown in Fig. 33 suggested the diagnosis of retroversion of an aortic cusp. The diastolic murmur in these tracings has a fundamental frequency of about 200 cycles per second. It is more intense and higher in pitch than the systolic murmur. Its configuration approximates an exponential decrement, which is a reduction in amplitude such as occurs when a tight string is plucked.

The phonocardiogram in Fig. 34 is taken from another patient in whom the diagnosis of retroversion of an aortic valve cusp was made. The diastolic murmur is of greater intensity than the second sound, from which it can be separated by a slight splitting effect. This murmur, like that in the previous case, has the decrement similar to that obtained by plucking a string.

The exact mechanism of the production of the musical diastolic murmur in these cases is not fully understood. It is almost certainly the valve cusp itself which undergoes vibrations initiated by the closure of the semilunar valves and maintained by the hemodynamics of the regurgitant stream for a greater or lesser time. It is interesting that a musical second sound may occur in the absence of aortic regurgitation or of retroversion of an aortic cusp. Such a case is illustrated in Fig. 35. This phonocardiogram was not considered to show a

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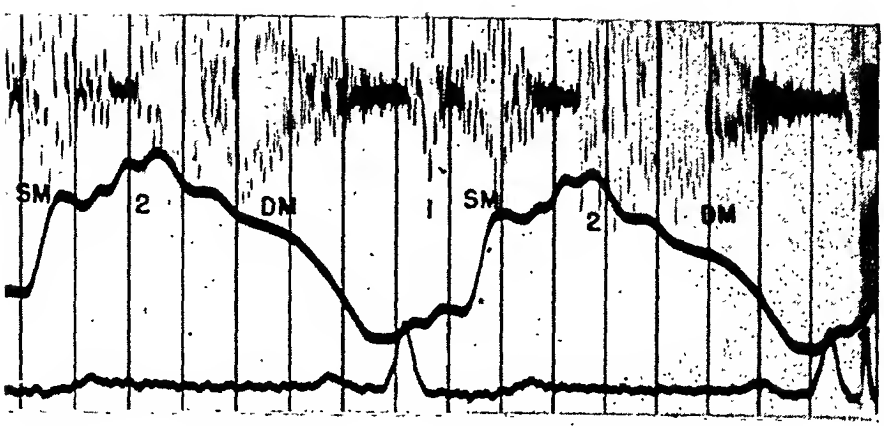

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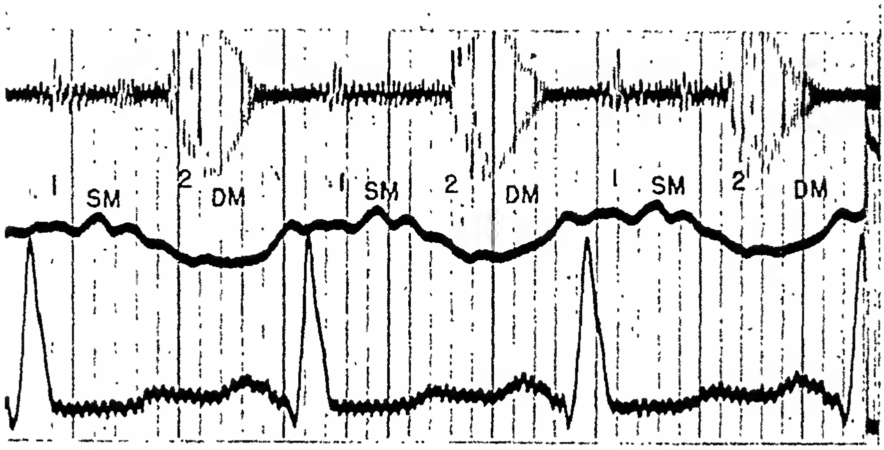

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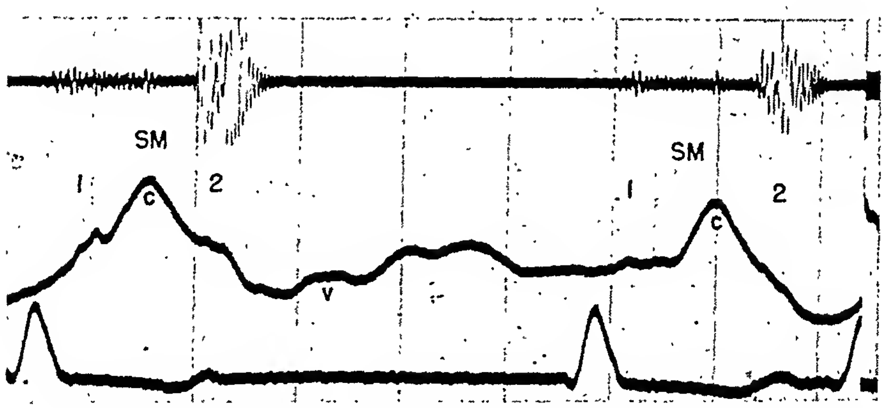

Fig. 33.—Woman, aged 21. Rheumatic heart disease following recurrent attacks of rheumatic fever since age 8. Aortic regurgitation diagnosed at age 11. Signs of retroversion of aortic cusp at age 19. Successful treatment of subacuto bacterial endocarditis at age 20, with increase in diastolic murmur. At time of phonocardiogram thrill accompanied Grade 5 diastolic murmur of whining, high-pitched character.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead II.

Fig. 34.—Man, aged 27. Rheumatoid arthritis since age 19. Musical diastolic murmur first heard at age 22, with little variation during last five years. Second sound metallic in quality followed by high-pitched musical diastolic murmur.

Upper tracing: logarithmic microphone with large open bell over second left intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

Fig. 35.—Woman, aged 54. Chronic pyelonephritis, uremia, congestive heart failure, auricular fibrillation, cardiac enlargement. Blood pressure, 140/90. Musical "cardboard door" second sound at aortic base, with no diastolic murmur.

Upper tracing: logarithmic microphone with large open bell over second right intercostal space. *Central tracing:* jugular pulse. *Lower tracing:* electrocardiogram, Lead I.

diastolic murmur, for the musical second sound terminated by the time of opening of the A-V valves, as judged by the apex cardiogram. However, the configuration of the sound is so similar to that found in the musical diastolic murmurs shown above that great care must be taken not to confuse the two. It is possible that this similarity may throw some light on the mechanism of their formation.

SUMMARY AND CONCLUSIONS

1. The ideal phonocardiograph should have the following characteristics:

a. Adequate sensitivity and deflection speed to record the faint, high-pitched murmurs encountered in auscultation.

b. A frequency response which enables sufficient amplification to register these murmurs without excessive deflections from vibrations of lower frequency. Such a response is present when the intensity of the vibrations undergoes the same modification with regard to frequency as occurs in the average stethoscope, in conjunction with the average hearing mechanism. This response has been termed "logarithmic."

c. An alternative frequency response, which will allow better reproduction of the lower frequency vibrations. This is available in the response which has been termed "stethoscopic."

d. Modifying characteristics that are obtained from the open bell and the Bowles diaphragmatic chestpieces, which may be added to either logarithmic or stethoscopic response.

2. Failure to comply with these requisites has resulted in inability to record the faint, high-pitched basal diastolic murmurs, and as a result there has been no adequate description of the graphic configuration of basal diastolic murmurs.

3. The physiological and physical factors concerned in the production of basal diastolic murmurs are discussed, in order that they may be related to the characteristics of the murmurs as recorded by the phonocardiograph.

4. The auscultatory characteristics of the basal diastolic murmurs are enumerated and a quality not previously brought to notice is described. This is a crescendo-decrescendo quality in early diastole which is sometimes obvious on auscultation but much more frequently demonstrated by phonocardiography.

5. A phonocardiographic technique which has proved satisfactory for the registration of all heart sounds and murmurs is described. By use of this technique all basal diastolic murmurs heard on auscultation can be recorded, with occasional registration of basal diastolic vibrations where no murmur was audible.

6. A method of standardization of the intensity of heart sounds and murmurs is described. This method is used in the illustrations.

7. Continuous murmurs caused by patent ductus, arteriovenous aneurysm, and venous hum are excluded from this study. The graphic configuration of other basal diastolic murmurs is illustrated by tracings from twenty patients with murmurs varying from very slight to loud in intensity. The characteristics of these murmurs are as follows:

a. The onset of the murmur can frequently be distinguished quite readily from the end of the second component of the second sound, although sometimes the two may be fused. The onset of the murmur may be separated from the second sound by a short silent interval or a series of lower frequency vibrations, due perhaps to the third component of the second sound. Such a delay is more frequently seen in murmurs of low intensity.

b. When the second sound is duplicated, the murmur is seen to come off one or other component of the sound. Such duplicated second sounds may represent asynchronism of closure of the semilunar valves. However, it is pointed out that, because of the variable onset and configuration of the diastolic murmur, it is unwise to assume that a murmur appearing to commence with the latter part of a duplicated sound is necessarily related to the semilunar closure that is delayed.

c. The frequency of the vibrations constituting the murmur varies in different cases from moderately low to high.

d. A purely decrescendo configuration is seen in only five of the twenty tracings. The other fifteen show to varying extents a crescendo-decrescendo configuration, with maximal intensity at or shortly after the time of the apex of the V wave in the jugular phlebogram.

e. The murmur sometimes ends in early diastole but in the majority of cases may be traced up to the first sound of the next cardiac cycle.

f. There is frequently a short period in late systole of comparative silence, in contrast to which the diastolic murmur is clearly evident.

8. The presence of a diastolic murmur is demonstrated in a patient who had on auscultation a very questionable murmur.

9. The differential diagnosis of a scratchy aortic diastolic murmur from a pericardial friction rub is made in another patient.

10. Vibrations of the base line may occur in diastole from extracardiac sources of activity. These vibrations should not be considered to be significant unless they show some period of maximal or minimal intensity which is related to the cardiac cycle, or some other obvious characteristic that is found in consecutive cardiac cycles.

11. Phonocardiograms of six patients are shown in which significant diastolic vibrations were recorded, although no murmur was heard on auscultation. The origin of these vibrations and the reasons they were not heard are discussed. The reasons are usually two, namely: (a) the low intensity of the vibrations with regard to their frequency; and (b) the fatiguing effect of a loud systolic murmur and second sound on the hearing mechanism.

12. The phonocardiogram of a loud and unusually low-pitched diastolic murmur found in a patient with pulmonary regurgitation is shown. Another unusual murmur believed, by auscultation, to be a mediastinal hum had, on phonocardiography, an early decrescendo phase suggestive of aortic or pulmonary regurgitation.

13. The phonocardiograms of three patients with retroversion of aortic cusps are shown. In one of these the characteristic loud murmur disappeared

under observation; this was considered to be evidence of spontaneous correction of the retroversion and confirmatory of the diagnosis.

14. The mechanism of production of the musical diastolic murmur in retroversion of an aortic cusp is discussed, and the similarity of the phonocardiogram to that of a musical second sound is noted.

15. When auscultation of a patient produces doubt or difference of opinion as to whether a basal diastolic murmur is present or not, this important question may be decided by an adequate phonocardiogram.

16. The configurations of the murmurs recorded show considerable variation but conform to certain distinct patterns.

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SOME EFFECTS ON THE CIRCULATION OF SMOKING CIGARETTES WITH VARYING NICOTINE CONTENT

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IT IS generally agreed that the smoking of cigarettes produces immediate changes in the circulation in practically all persons. The effects are shown by an increase in heart rate and blood pressure as well as by constriction of the peripheral vessels.[1] In some patients the occurrence of vasospasm has been reported in coronary and retinal arteries.[2,3] Variability in the degree of response in different subjects depends to a greater degree on individual susceptibility to tobacco than on the presence of cardiovascular disease.[4] Most investigators have ascribed to the nicotine in the smoke the chief role in producing these vascular reactions.[5,6,7] Some, however, still question its importance in this respect, and the suggestion has been made that sympathetic stimulation brought about by the irritating action of the smoke upon the respiratory tract may be responsible for the changes noted.[8] Others have attributed the effects to deep breathing.[9]

Such varying opinions leave the issue still unsettled. Because the matter is of some practical importance, particularly for patients with cardiovascular diseases, this study was planned.

MATERIAL AND METHODS

Observations were made on seventeen subjects. In nine, no cardiovascular disease was present. Of these, three were men and six were women. Their ages ranged from 22 to 56, with an average of 34 years. There were eight patients with cardiovascular disease, of whom six were men and two were women. Their ages ranged from 34 to 57, with an average of 47 years. In six, the diagnosis was coronary heart disease with anginal pain; one of these also had hypertension and three showed evidence of healed cardiac infarction. There was one instance of inactive rheumatic heart disease with aortic regurgitation and one of peripheral vascular disease of the Raynaud type.

In each subject the following procedures were carried out: (1) smoking, in succession, two regular cigarettes containing approximately 2 per cent of

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nicotine in the tobacco; (2) smoking two "low nicotine" cigarettes containing 0.23 per cent of nicotine*; (3) intravenous injection of 2.0 mg. nicotine bitartrate containing 0.6 mg. of the alkaloid†; (4) smoking two cubeb cigarettes containing no nicotine.‡ In a number of individuals, observations were repeated after the smoking of the regular cigarette and after the intravenous injection of nicotine.

All subjects were habitual smokers and inhaled. The regular cigarettes were of the standard commercial types and varied with the choice of the smoker. The cigarettes of low nicotine content were made from Burley tobacco naturally low in nicotine.[10] They contained approximately one-ninth as much nicotine as the standard brands. Cubebs were chosen in preference to some of the types of cigarettes free from nicotine which have been employed by other workers because they are not as irritating to the respiratory mucous membranes as are those containing ash-free filter paper and, unlike those made of corn silk, are commercially available. Furthermore, no effect on the circulation is attributed to cubeb.

The following was the routine followed. Quiet was maintained in the room in which the observations were made to avoid the occurrence of any distractions which might exert a reflex influence on the circulation. Only a single procedure was carried out on any one day. The subject rested for thirty minutes in a semirecumbent position on a comfortable hospital bed. Control readings of heart rate and of systolic and diastolic blood pressures were taken and recorded every minute for a period of ten minutes. Then two cigarettes were smoked in succession and inhaled at the patient's own chosen rate of puffing. The usual length of the smoking period was from twelve to fifteen minutes. During this period and for thirty minutes thereafter, readings of heart rate and blood pressure were continued.

The same preliminary observations were made prior to the intravenous injection of nicotine.[11] A sheet was hung before the face of the subject to obscure his view of the proceedings. Procaine was injected into the skin before the control readings were taken to avoid pain on insertion of the infusion needle. After the needle was in place, normal saline was allowed to run in slowly and after ten minutes, during which readings of heart rate and blood pressures were taken as described, 2.0 mg. of nicotine bitartrate in 3.0 c.c. of normal saline was injected through a three-way stopcock at the rate of 1.0 c.c. per minute. The subject was unaware of the shift from saline to nicotine. Observations of heart rate and blood pressures were continued for thirty minutes after the injection was completed.

For each type of stimulus, the effects were expressed as the maximal differences between the control levels and those observed after the stimulus was applied.

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*Dr. H. B. Haag, Professor of Pharmacology, Medical College of Virginia, Richmond, kindly supplied the cigarettes with low nicotine content. The tobacco of commercially "denicotinized" cigarettes contains approximately 1 per cent of nicotine.

†Nicotine bitartrate in aqueous solution was supplied in ampoules by the Abbott Laboratories, through the courtesy of Dr. J. F. Biehn.

‡According to the manufacturer's label, these are composed of 80 per cent cubeb and 20 per cent inactive herbs added to obtain suitable burning qualities.

AMOUNT OF NICOTINE ABSORBED

The average American cigarette contains about 20 mg. of nicotine or 2 per cent by weight. According to Haag and Larson,[12] when a cigarette is puffed to butt length in the ordinary way, 22 per cent of the "main-stream" smoke, containing approximately 3.0 mg. of nicotine, is drawn into the mouth. In the noninhaler, from 67 to 77 per cent is absorbed.[13,14] On inhalation from 88 to 98 per cent is taken into the blood stream through the mucous membranes of the respiratory tract.[12,13,14]

Assuming 95 per cent absorption by inhalers, the amount of nicotine taken into the body from the smoke of one regular cigarette is about 2.85 milligrams. In the case of the low-nicotine cigarette, it is approximately 0.32 milligrams.* Thus, the amount absorbed from the low-nicotine cigarette was about one-ninth of that obtained from a regular cigarette and one-half as much as was injected, in terms of alkaloid, directly into the circulation.

All of the smokers remarked that both the low-nicotine cigarettes and the cubebs were unpleasant to taste and were more irritating to the mucous membranes than the regular cigarettes. Consequently, if either of these factors was responsible, in whole or in part, for inducing changes in the circulation, these should have been more pronounced when the nicotine content of the tobacco was low or when no nicotine was present. That this was not so will become clear.

RESULTS

The figures obtained were submitted to statistical analysis.† It was at once evident that there were no significant differences between the normal group and the group with cardiovascular disease, either in level of effect or in changes in that level from one type of stimulus to another. Accordingly, the results have been expressed as the combined averages of the seventeen subjects, computed by using only the first reading for those on whom the observations were repeated (Table 1).

TABLE I. COMBINED AVERAGES AND RANGES, IN SEVENTEEN SUBJECTS, OF MAXIMAL INCREASES IN HEART RATE AND BLOOD PRESSURES‡

STIMULUS	HEART RATE		SYSTOLIC		DIASTOLIC	
	AVERAGE	RANGE	AVERAGE	RANGE	AVERAGE	RANGE
Regular cigarette	15.5	4–30	14.7	8–26	11.4	6–18
Low-nicotine cigarette	9.4	0–21	8.0	0–28	5.4	0–12
Intravenous nicotine	8.5	0–32	8.0	0–25	6.0	0–19
Cubeb cigarette	3.0	4–10	3.9	0–14	2.8	0–10

‡In computing averages, the figures used for those individuals having more than one observation were only those obtained in the first series of readings.

*Personal communication from Dr. H. B. Haag, who determined the nicotine content by analysis of the smoke.

†We are indebted to Dr. John W. Fertig, Professor of Biostatistics, College of Physicians and Surgeons, Columbia University, for making the statistical analyses.

The average increase in heart rate, after the smoking of regular cigarettes, was 15.5 beats per minute; after the smoking of low-nicotine cigarettes, it was 9.4; after the intravenous injection of nicotine, it was 8.5; and after the smoking of cubebs it was 3 beats per minute.

The average rise in systolic pressure, after the smoking of regular cigarettes, was 14.7 mm. Hg; after the smoking of low-nicotine cigarettes, it was 8; after the intravenous injection of nicotine, it was 8; and after the smoking of cubebs, it was 3.9. In like sequence, the average rises in diastolic pressure were 11.4, 5.4, 6.0, and 2.8 mm. of mercury.

It is apparent that the regular cigarettes cause a significantly larger reaction, on the average, than any of the other three stimuli. The cigarettes with low nicotine content have a larger average effect than the cubebs. In the case of systolic and diastolic blood pressures, the difference between these two types of cigarettes is only of borderline significance; that is to say, it is not clearly established. The intravenous injection of nicotine produces effects not significantly different from those caused by the smoking of low-nicotine cigarettes.

By utilization of the repeat observations for regular cigarettes and for the intravenous injection of nicotine made in both this study and those published in previous papers from this laboratory,[4,11] it is possible to obtain a measure of the amount of variation within individuals. In this way, the meaning of each individual's response can be assessed. After smoking regular cigarettes, practically all individuals are reactors in the sense that the amount of change in heart rate and in systolic and diastolic blood pressures is greater than can be ascribed to chance fluctuations within the individual. After smoking the low-nicotine cigarettes or after the intravenous injection of nicotine, very few of the individuals can definitely be regarded as reactors with respect to any of the three measured effects.

By using the same measure of within-individuals variation just described it can be determined whether the individuals are significantly differentiated from each other with respect to the magnitude of the response. Only in the case of heart rate are they so differentiated, as indicated by the fact that the variation between individuals is greater than that within them. For this reason, single readings of the rise in heart rate serve to distinguish between individuals and so may be used as an index of variations in sensitivity to nicotine.

The variation within individuals, which is the basis for judging the statistical significance of each individual's reaction, is quite large. In the case of the heart rate, a change of less than 9 beats per minute could be explained as a chance fluctuation from zero. In the case of the systolic pressure the critical value is 10 mm. Hg and in the case of the diastolic it is 8. Whereas, in a statistical sense, these critical values are valid, from the clinical standpoint, sensitivity must be measured on a more conservative basis. Inasmuch as only changes in heart rate appear to differentiate between individuals in the case of the regular cigarette, and fluctuations up to 30 beats have been encountered, it is suggested, arbitrarily, that an increase of more than 25 beats per minute, after the smoking of a regular cigarette, may be regarded as a sign of hypersensitivity to nicotine. In the

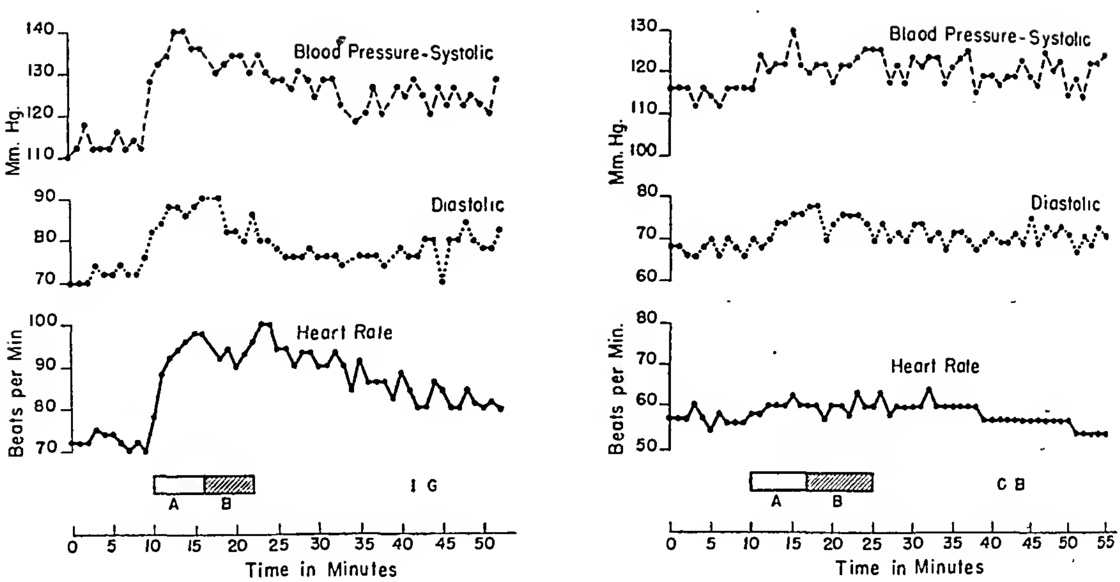

Fig. 1.—Smoking regular cigarettes. Subject I. G., 47-year-old man with coronary heart disease and anginal pain. *A*, Smoking first cigarette; *B*, second cigarette. The response is that of a hypersensitive subject. Subject C. B., 58-year-old man with no cardiovascular disease. *A*, First cigarette; *B*, second cigarette. The response is within the normal range.

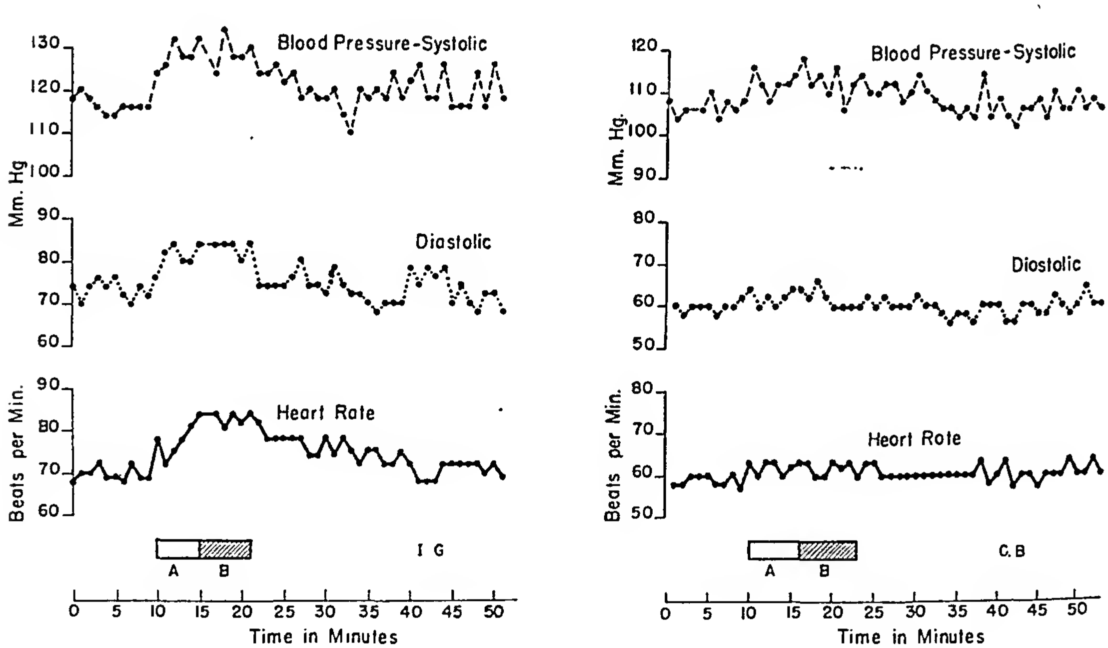

Fig. 2.—Smoking cigarettes containing 0.23 per cent nicotine. Subject I. G. *A*, First cigarette; *B*, second cigarette. Subject C. B. *A*, First cigarette; *B*, second cigarette.

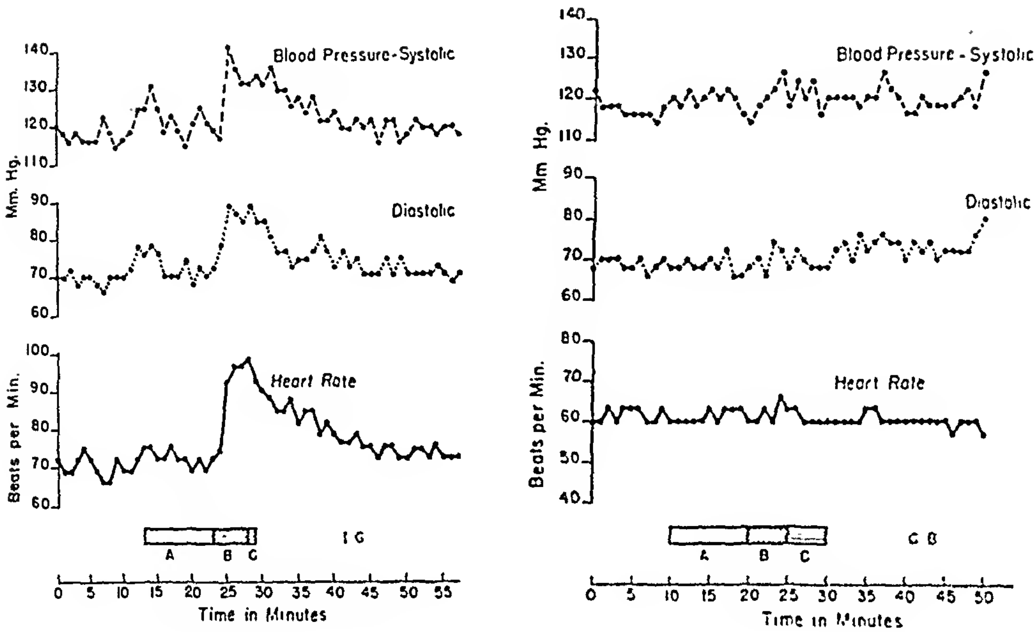

Fig. 3.—Intravenous injection of nicotine. Subject I. G. *A*, Injection of physiologic salt solution; *B*, injection of 2 mg. nicotine bitartrate; *C*, injection of salt solution. Subject C. B. *A*, Injection of physiologic salt solution; *B*, injection of 2.0 mg. nicotine bitartrate; *C*, injection of salt solution.

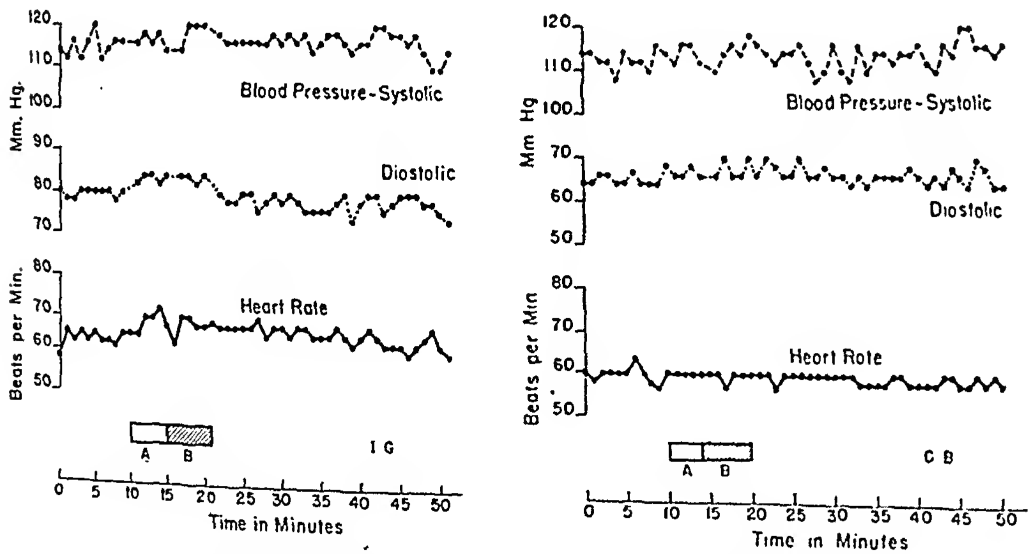

Fig. 4.—Smoking cubeb cigarettes. Subject I. G. *A*, First cubeb; *B*, second cubeb. Subject C. B. *A*, First cubeb; *B*, second cubeb.

present study, a rise of 30 beats was not exceeded in any instance, although greater increases have been reported by us in an earlier paper,[4] and by others.

Almost invariably, the maximal effects occurred after the smoking of the first cigarette; in no case, after the second, was the height of the reaction significantly increased. Within the limits of two cigarettes, therefore, there was no evidence of cumulative action.

Examples of the responses obtained to the four types of stimulus are shown graphically in Figs. 1, 2, 3, and 4, in a hypersensitive subject and in one reacting normally. The differences in levels, with respect to both stimulus and individual sensitivity, are readily apparent.

SUMMARY AND CONCLUSIONS

1. The immediate effects on the circulation of smoking regular cigarettes are due to the nicotine in the tobacco.

2. In the individual, the degree of reaction varies directly with the nicotine content of the smoke.

3. Variability in response in different persons depends to a greater extent on individual susceptibility than on the presence of cardiac disease.

4. Single measurements of the rise in systolic or in diastolic blood pressure do not serve to distinguish differences in sensitivity between individuals.

5. Acceleration of heart rate is the most sensitive index of effect. Differentiation between individuals is possible on the basis of a single reading.

6. Smoking cigarettes with nicotine content as low as 0.23 per cent, which is one-ninth of that present in the average regular cigarette, causes a significant increase in heart rate. This increase is of the same order of magnitude as that produced by the intravenous injection of 0.6 mg. of nicotine alkaloid.

7. It is suggested that, after the smoke of one regular cigarette has been inhaled, an increase in heart rate of more than 25 beats per minute may be regarded as an index of hypersensitivity to the immediate effects of nicotine.

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Abstracts

Third Inter-American Cardiological Congress

A STUDY OF DIFFERENTAL DIAGNOSIS IN AORTIC REGURGITATION.—S. ACEVES, M.D., D. A. CANEPA, M.D., and A. LIMÓN LASON, M.D., Mexico, D. F., Mexico.

The material used is from the National Institute of Cardiology of Mexico. After a brief analysis of all the cases of aortic insufficiency studied in this institution and after pointing out the errors in diagnosis, the study of 143 cases of aortic insufficiency is presented. The incidence of syphilis, rheumatism, atheroma, and other causes of aortic insufficiency is given. The past history, age, sex, time of onset, clinical picture, and evolution are analyzed, together with the coincidence of subacute bacterial endocarditis and the causes of death. Special attention is paid to the importance of the diastolic murmurs at the apex. In some cases these murmurs were a decisive factor in the diagnosis, while in others they were a cause of confusion. An analysis of the electrocardiographic and roentgenographic data is made, and the elements which incline the diagnosis toward syphilis or rheumatism are pointed out. The clinical findings are compared with the findings at autopsy.

THE IMPORTANCE OF PRECORDIAL LEADS TAKEN ABOVE THE CONVENTIONAL POSITIONS IN FOLLOWING THE EVOLUTION OF MYOCARDIAL INFARCTION.—RAFAEL M. ALZAMORA, M.D., and AUGUSTO MISPIRETA, M.D., LIMA, PERU.

Abstract in English not available.

SOME OBSERVATIONS ON THE HUMAN ELECTROCARDIOGRAM FOLLOWING CHANGES OF ALTITUDE ENVIRONMENT.—RAFAEL ALZAMORA, M.D., and CARLOS MONGE M., M.D., LIMA, PERU.

The electrocardiogram of man acclimatized to high altitude since prehistoric time has been studied by Monge, Saenz, Rotta, and Kerwin. Its most important characteristics are: increase in the frequency of deviation of A_{QRS} toward the right and increase of the vertical electric position of the heart. Moderate exercise resulted in inversion of the P wave, shortening of P-R, deviation of S-T, and bradycardia instead of acceleration.

We have studied electrocardiographic variations in a group of soldiers born at 10,500 feet (Huancayo), sent to 14,900 feet (Morococha) for fifteen days, and brought down to sea level (Lima).

In Morococha there was often S-T elevation and T inversion in several precordial leads. On arrival at sea level, T became normal. Further observations showed a progressive increase of QRS and T amplitude in nearly all leads, a gradual shift of the electrical axis toward the left, and a tendency for the heart to become horizontal. These modifications suggest that marked changes in the electrical activity of the heart are probably related to the physiological and chemical variations to which these soldiers were subjected. Throughout the observations the men behaved like normal subjects.

TREATMENT OF PROGRESSIVE NON-MALIGNANT HYPERTENSION IN THE OLDER AGE GROUP.—J. S. Arnason, M.D., Seattle Wash.

The results of treatment for a period of one year of eighty patients with progressive nonmalignant hypertensive disease are presented. In the group were twenty-five men and fifty-five women. The average age was 56 years for men and 62 years for women. The ages varied from 47 to 83 years. Maximum pressure recorded was 265/150, the minimum 175/90. Of these, 4 per cent showed aggravation of symptoms, with increase rather than decrease in blood pressure; 6.67 per cent showed only slight improvement; 89.37 per cent were improved. Individual and composite results are shown.

All patients without serious complications were encouraged to work since the unfavorable psychological effects of enforced idleness and the resultant continued worry was more harmful than ordinary occupation. Careful, complete examination was made and a suitable plan of treatment for each individual was worked out with special emphasis on the following: home conditions, personal habits, recreation, occupation, physical defects, diet, drugs, and frequent and continuous checkups and consultations with the physician over a period of months. Complications were briefly considered.

The results seem to compare favorably with those obtained by surgical means for this type of hypertension. The method is safer and much less expensive.

A NEW METHOD FOR THE FUNCTIONAL INVESTIGATION OF THE PERIPHERAL BLOOD-VESSELS.—Eugene Barath, M.D., Budapest, Hungary.

The functional investigation of the peripheral blood vessels plays an important role in the early diagnosis of circulatory disturbances. A new method is presented consisting in the registration of the oscillometric curves after the injection of a vasoconstrictor drug, ergotamine, 0.5 mg., and a vasodilator drug, like sodium nitrite, 0.10 Gm., dihydroergotamine, or dihydroergocornine, 0.5 milligram.

The values of the oscillometric measurements are recorded on the ordinate and the corresponding blood pressure, on the abscissa. The measurements are made on all four extremities. A decrease of the oscillatory waves after ergotamine is found in patients with increased vasospastic tone. This is often also a precursor of later coronary disease and a sign of the progressing character of the cardiovascular disease. In these patients the vasodilatation after nitrite and dihydroergocornine is often totally absent. The absence of any dilatation or constriction points to severe pathologic changes in the arterial system (torpor vascularis). Good reaction of the blood vessels with only one-sided, slight decrease of the oscillation is often a sign of beginning or benign arterial disease.

The practical importance of these methods lies in the possibility of detecting arterial and also coronary diseases in the early stage.

THE PRECOLLAGEN NETWORK OF THE HEART VALVES DURING ACTIVE RHEUMATIC FEVER.—R. Barroso-Moguel, M.D., Mexico, D. F., Mexico.

This paper deals with the role of connective fibers and undifferentiated mesenchymatous cells in rheumatic lesions of the mitral valve.

The most important findings refer to the precollagen fibrils (reticular, argyrophilic fibrils). The morphological and histochemical properties of the precollagen fibrils of the heart valves are conceived to be between those of the collagen bundles in the loose connective tissue and of the reticular network in

the hematopoietic organs. Thus, these fibrils are similar to the first fibrillar structure of the embryonal mesenchyme. When Aschoff nodules are present in the superficial verrucosities of fresh fibrin, the precollagen fibrils increase in number and in argyrophilia and penetrate into the lesions; a similar reaction is present in all nonrheumatic alterations of allergic nature. The undifferentiated mesenchymatous cells appear as polyblasts in rheumatic valvular lesions.

These results have been obtained with the techniques of silver impregnation of Rio-Hortega.

INTRACARDIAC BLOOD PRESSURE IN HUMAN SUBJECTS AND ITS RELATION TO THE RESPIRATORY PHASES.—A. Battro, M.D., H. Bidoggia, M.D., E. Pietrafesa, M.D., and F. Labourt, M.D., Buenos Aires, Argentina.

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THE EFFECT OF HYPOPOTASSEMIA ON THE ELECTROCARDIOGRAM. CORRELATION WITH CLINICAL AND CHEMICAL STUDIES.—Samuel Bellet, M.D., Carl S. Nadler, M.D., Peter Gazes, M.D., and Mary Lanning, A.B., Philadelphia, Pa.

The electrocardiographic findings in hyperpotassemia, particularly as they occur in azotemia and Addison's disease, are fairly well known. However, there are comparatively few reports on the effects of hypopotassemia. The object of this communication is to report our observations in hypopotassemia in various clinical states including the following: (a) forty-five cases of diabetic acidosis, (b) fifteen cases of vomiting due to intestinal obstruction, and (c) conditions associated with diarrhea and fluid loss.

These studies consisted of electrocardiographic and simultaneous chemical studies, including serum potassium, calcium, sodium, pH, chlorides, and carbon dioxide combining power. These patients were followed serially during their stay in the hospital. The effects of the administration of potassium and calcium in these patients were noted and correlated with the clinical, chemical, and electrocardiographic findings. The electrocardiographic alteration observed in hypopotassemia reverted to normal following the administration of potassium, and improvement in the clinical state was observed.

The role of the electrocardiogram in revealing alterations in the serum potassium is emphasized. The various patterns observed in hypopotassemia are discussed in detail. Statistical correlations were made between the potassium level and alterations in the amplitude of the T waves and Q-T segment. The implications from the standpoint of therapy in these various states are discussed.

THE VALUE OF RICE DIET IN THE TREATMENT OF ESSENTIAL ARTERIAL HYPERTENSION.—Isaac Berconsky, M.D., and Abraham Cohan, M.D., Buenos Aires, Argentina.

Rice diet was given to fifty-eight ambulatory patients with essential hypertension. The results in seventeen patients were not considered because they precociously gave up the diet, or followed it irregularly.

The changes of blood pressure in the forty-one who strictly continued the diet during 16 to 180 days are as follows: In twenty-six cases (63.4 per cent) there was a decrease from 1 to 24.5 mm. Hg in the mean arterial pressure (systolic and diastolic); in fourteen cases (34.1 per cent), a rise from 1 to 18.4 mm. Hg; and in one case there was no change. According to Kempner's criterion, we may consider three patients to have been improved (7.3 per cent) be-

OBSERVATIONS ON FATTY INFILTRATION OF THE MYOCARDIUM.—William A. Brams, M.D., and Kurt Biss, M.D., Chicago, Ill.

It has not yet been established that fatty infiltration of the myocardium can result in significant clinical manifestations or that it may lead to serious consequences. The literature pays scant attention to this subject and most modern textbooks on cardiology dismiss it with few words.

Significant fatty infiltration occurred in 6 per cent of adults among 5,831 autopsies. The right ventricle was involved alone or predominantly in 90 per cent and both ventricles equally, in 10 per cent; there was no instance of isolated left ventricular involvement. Body weight was not a factor, but fatty hearts were present in the majority of patients who had diabetes, gall bladder disease, or disease of the liver or pancreas. Seven cases with sudden death are reported: two patients had congestive failure, and one had paroxysmal tachycardia; death was unexpected in four others. Patients with fat-infiltrated hearts withstand surgery poorly; there is a tendency to sudden death. No distinctive clinical manifestations occur. It apparently simulates other forms of diffuse myocardial disease.

The object of this report is to awaken interest in the subject so that more material and further study might lead to the establishment of a clinical picture.

CHANGES IN THE FRONTAL AND SAGITTAL ELECTROCARDIOGRAM OF HYPERTENSIVE SUBJECTS DURING AN EXPERIMENTALLY PRODUCED PHASE OF LOWERED BLOOD PRESSURE.—J. Brumlik, M.D., and C. E. Kossmann, M.D., New York, N. Y.

Regression of changes in the so-called "typical electrocardiogram" of essential hypertension, sometimes occurring spontaneously or as observed after the use of nitrites, potassium salts, and lumbar sympathectomy, have attracted considerable attention. Because of the clinical importance attached to this phenomenon, especially after treatment, an attempt was made to produce it by another method.

A temporary reduction of blood pressure was obtained in fifteen patients with essential hypertension by the intravenous administration of typhoid vaccine. The usually associated rise in temperature was partly or completely eliminated by premedication with aminopyrine. During the period of lowered blood pressure the changes observed in standard and special electrocardiographic leads (including the sagittal leads of Arrighi) can be summarized as follows:

The mean electrical axis of QRS and of QRS-T was deviated slightly to the right or was not affected at all. Variations in the order of ventricular repolarization caused a decrease in positivity or an increase in negativity of the T wave chiefly in Lead I. Similar changes were sometimes observed in certain of the sagittal leads only.

Conclusion.—The observed electrocardiographic changes demonstrate that a sudden and transient fall in blood pressure induced by intravenous pyrogen does not make the "hypertensive electrocardiogram" assume a more "normal" appearance, but, on the contrary, makes it assume a more abnormal configuration.

PENETRATING WOUNDS OF THE HEART. CLINICAL, RADIOLOGICAL AND ELECTROCARDIOGRAPHICAL STUDY. — Frank Canosa Lorenzo, M.D., Havana, Cuba.

We have studied from a clinical, radiological, and electrocardiographical point of view, patients presenting penetrating wounds in the heart caused by knife or bullet. Exclusively pericardial lesions are not included in this report.

Most of the patients had parietal wounds which only touched the muscle. In two patients the wound entered a cavity of the heart. In a patient wounded by a bullet, a free passage between the pericardium, pleural cavity, and the exterior was established with considerable hemorrhage. In four cases a rapid accumulation of blood in the pericardiac cavity produced the syndrome of acute cardiac compression. A hemopericardium appeared slowly in one patient causing chronic heart tamponade.

In all of these pateints paracentesis of the pericardium was performed, not only as a diagnostic method but for treatment. The radiological examination in this series was useful and interesting. The electrocardiogram gives us knowledge of involvement of the heart. The use of the multiple unipolar precordial leads in our study shows great superiority over the use of only a single precordial lead for the diagnosis of the myocardial lesion and its location.

UPPER ABDOMINAL PAIN AND ANGINA PECTORIS. — George D. Capaccio, M.D., Seattle, Wash.

Factors concerned with anginal pain, coronary sclerosis, and upper abdominal disorders, such as gallbladder disease, chronic peptic ulcer, and other conditions, are discussed. An attempt is made to clarify the interrelationship of this controversial subject. The altered coronary blood flow from reflex change is accepted but the added feature in the production of anginal pain is the supposition that upper abdominal pain acts *also* in the same capacity as overexertion or excitement in initiating an anginal episode.

A representative case is reported of a woman of 60 years with coronary sclerosis, angina pectoris, and pain in the upper abdomen due to a penetrating, stenosing, duodenal ulcer. A subtotal gastric resection and partial duodenectomy was performed which was followed by an uneventful convalescence, immediate disappearance of all pain, and subsequent absence of both types of distress on a moderately restricted regime.

It is the opinion of the author that the severe pain of the ulcer acted not unlike overexertion in imposing an additional load upon a heart already affected by coronary sclerosis. This symptom complex of pain in the upper abdomen followed by anginal distress was interrupted by surgery.

THE DIAGNOSIS OF SEPTAL DEFECTS BY MEANS OF THE LEVO-ANGIOCARDIOGRAM.—Agustin Castellanos, M.D., Havana, Cuba.

Some authors believe that angiocardiography has no value as an aid in the diagnosis of interauricular and interventricular communications.

Some years ago, we published an article pointing out the direct and indirect signs obtained by means of dextroangiocardiograms in Roger's disease. In cases of interauricular communication the following dextroangiocardiographic images are obtained: (1) When the septal defect is small, opacification occurrs only at the left auricle. In such a case the normally clear space between the lower end of the superior vena cava and the pulmonary artery trunk, in anteroposterior position, disappears, and it is seen to be quite opaque. (2) When the septal defect is large, there is a total radio-opacification of the heart (cast-image).

It is true that in some cases of septal defects we may obtain a normal dextroangiocardiogram; and that is the reason why some years ago we applied the levoangiocardiogram, which is always of great value, because in such types of defect the blood pressure at the left cavities is higher than that in the right cavities, and the opaque material passes from left to right. In a normal levoangiocardiogram, no opaque material appears within the right cavities and the

pulmonary artery. In cases of interauricular communication, there is radio-opacification of the left cavities and aorta, and also of right auricle and ventricle. In cases of interventricular communication, besides the left cavities and aorta, there is opacification of the right ventricle and the pulmonary artery. The method is useful for getting an idea of the size of the septal defect. If the septal defect is very large, the pulmonary artery is more opaque than the aorta. If there is a small defect, the reverse is true.

The differential diagnosis between interauricular and interventricular communication consists in the radio-opacification of the right auricle, which occurs in cases of interauricular defect, whereas in cases of interventricular defect there is no radio-opacification of the right auricle. In this fact lies the importance of the oblique positions.

DYNAMIC MODIFICATIONS OF THE RIGHT VENTRICLE ANGIOCARDIOGRAPHICALLY STUDIED.—ALEJANDRO CELIS, M.D., ENRIQUE ARCE GOMEZ, M.D., and H. CASTILLO, M.D., MEXICO, D.F., MEXICO.

The paper describes the technique used by one of us (A. Celis) for the purpose of obtaining the exclusive angiocardiographic picture of the right ventricle. The triangular form of the diastolic picture in the postero-anterior position is discussed. Its borders are described and its relations to those of the cardiovascular silhouette are pointed out. The dynamic modifications of the right ventricle during its contraction are studied. The picture of the right ventricle in the left transverse position and its dynamic alterations are analyzed. The presence of a residual opaque substance (incomplete emptying of the right ventricle) is mentioned. The described modifications are discussed.

SALICYLATES. NEW PHARMACOLOGICAL ASPECTS WITH A VIEW TO THEIR USE IN RHEUMATIC FEVER.—TEODORO E. CESARMAN, M.D., and SALVADOR MARTÍN, Q.F.B., MEXICO, D.F., MEXICO.

This study attempts to demonstrate that the beneficial effects of sodium salicylate and acetylsalicylic acid are products of slow elimination. It is based on work done with rheumatic fever patients of the National Cardiological Institute of Mexico and with healthy individuals.

A new method of estimating the salicylate content in the blood is used. The exactness of the method is demonstrated and a comparison is established between it and the one used by Coburn. Sodium salicylate and acetylsalicylic acid administered every twelve hours were capable of producing, in a short time, a sustained blood level. The drug was administered in doses of 0.10 Gm. per kilogram of body weight in twenty-four hours (two doses of 0.05 Gm. per kilogram every twelve hours) and the concentrations obtained ranged between 332 and 561 gamma. Higher concentrations were obtained when the doses were administered twice every twenty-four hours than when the salicylates were given in six or eight divided doses. On the administration of moderate quantities of alkali, no important modification in the blood concentration of salicylates was noticeable.

A preliminary report is made on the role played by the hematocrit in the blood concentrations of salicylate and some other products.

SURGICAL TREATMENT OF HYPERTENSIVE HEART DISEASE AND OF HEART FAILURE OF HYPERTENSION.—IGNACIO CHÁVEZ, M.D., and LUIS MÉNDEZ, M.D., MEXICO, D.F., MEXICO.

Published in full in this issue.

TREATMENT OF PERIPHERAL VASCULAR DISORDERS BY TRANSFER OF IONS OF MECHOLYL.—Nicandro Chávez, M.D., Mexico, D.F., Mexico.

Three thousand one hundred five treatments were given to 103 patients. In every case, oscillometric readings and the temperature at the distal end of the fingers were taken before, just after, and two hours after treatment. Mecholyl solutions were used at different concentrations until toxic symptoms developed with high dosage. The optimum concentration was 1 per cent. With this dose, gradual and increasing temperature and oscillometric curves were observed. In cases of organic occlusion these findings do not change. On the other hand, the collateral circulation improves considerably. The treatment can be given daily, for long periods of time with absolute tolerance by the patient.

THE UNIPOLAR LEADS OF THE ELECTROCARDIOGRAM IN RIGHT VENTRICULAR ENLARGEMENT.—Juan Codina-Altés, M.D., and Carlos Pijean de Beristain, M.D., Barcelona, Spain.

The electrocardiographic changes observed in right ventricular enlargement are probably due to two distinct factors: (1) increase in thickness of the right ventricular wall and (2) changes in the position of the heart. The characteristic change of the hypertrophy is the increased amplitude of the R wave and diminution of the S wave in the right thoracic leads. This may lead to a complete disappearance of S and the presence of a high R wave, which may be preceded by a small Q wave. Changes in the position of the heart are manifested by a deep S wave in the left thoracic leads. In these, the QRS group may become predominantly negative. The same position changes account for the late positivity of aV_R and for the fact that aV_L becomes deeply negative. When the heart enlargement is only slight or moderate, aV_F resembles the left thoracic leads. When the hypertrophy extends itself to the inflow tract of the right ventricle, the potential variations originating in this chamber are transmitted not only to the right side of the precordium but also to the left leg, and aV_F resembles V_1 and V_2.

The RS-T and T-wave changes are not, as a rule, important. In lead V_6, T is always positive and in aV_R, always negative.

THE UNIPOLAR LEADS OF THE ELECTROCARDIOGRAM IN LEFT VENTRICULAR ENLARGEMENT.—Juan Codina-Altés, M.D., and Carlos Pijean de Beristain, M.D., Barcelona, Spain.

The characteristic modifications of the unipolar leads of the electrocardiogram in left ventricular enlargement are: (1) increased negativity of the right thoracic leads, (2) increased positivity of the left thoracic leads, (3) sudden shift between the QRS groups registered at the right side of the precordium and those obtained at the left side, (4) displacement to the left of the point at which the highest R wave may be registered, (5) possibility of a higher R wave in Lead V_6 than in V_4, and (6) increased amplitude of the QRS group. A Q wave is often registered in the left positions, a useful point in differentiating left bundle branch block.

Because of changes in the position of the heart, Lead aV_L resembles the left thoracic leads and aV_F the right ones. This is traduced in the standard leads by a "left axis deviation." These position changes are not always present and the heart may remain in a more or less vertical situation. In these cases, nevertheless, the thoracic leads show the same typical changes.

The RS-T segment tends to become elevated in Leads V_1, V_2, and aV_R and depressed in V_4, V_5, V_6, and aV_L. In the first of these leads, T tends to be positive and in the second ones, negative.

THE ENDOCARDIAL ELECTROCARDIOGRAM UNDER PATHOLOGICAL CONDITIONS OF THE PERICARDIUM AND OF THE MYOCARDIUM.—E. Coelho, M.D., J. M. Fonseca, M.D., and Adelaide Constantino, M.D., Lisbon, Portugal.

The intracavity potential of the dog in certain experimental conditions was studied with the unipolar derivations. The electrodes were introduced in the right cavities through the jugular vein, and in the left ventricle, through the carotid artery. The procedure consisted in altering the pericardial surface, provoking in some experiments generalized pericarditis and in others partial necrosis of the wall, without reaching the endocardium. In pericarditis as well as in the partial necrosis of the wall of the heart (always with pericarditis epistenocardica), the fundamental alterations of the electrocardiogram consisted in depression of RS-T segment, more or less intense, and deep negativity of the T wave. Lengthening of QS in the final period of the experiment was also observed. We could not obtain characteristic records of localization, except when we interfered with the posterior wall and reached the septum (producing lesions of the bundle of His). The electrocardiographic alterations of the two series of experiments were studied immediately and some days after the operation.

EXPERIMENTALLY PRODUCED CORONARY ARTERY INSUFFICIENCY, CORONARY ARTERY SPASM, AND A DEMONSTRATION OF THE REMARKABLE RESERVE POWER OF THE HEART.—Eliot Corday, M.D., Ramon Spritzler, M.D., H. C. Bergman, Ph.D., H. E. Krueger, M.D., and Myron Prinzmetal, M.D., Los Angeles, Calif.

This subject is discussed in this issue.

SURGICAL TREATMENT OF THE CARDIAC LUNG.—P. Cossio, M.D., and I. Perianes, M.D., Buenos Aires, Argentina.

After emphasizing the importance of the cardiac lung in clinical heart disease, the authors conceived the possibility of the surgical control of the lung engorgement by left ventricular failure or mitral stenosis, when the condition cannot be controlled by the classical medical treatment.

With this object several surgical procedures on dogs were performed, some of them designed to drain the lungs (anastomosis of pulmonary veins and other vessels of the systemic circuit) and others to reduce the output of the right ventricle (tricuspid insufficiency produced by valvulotomy through the internal jugular vein with an instrument which also permits the measurement of the intracardiac pressure and ligation of the inferior vena cava below the renal veins, according to the retroperitoneal technique in use).

Once the technique was developed and assurance obtained that human subjects could tolerate both procedures, first one and then the other, or only one, .ere practiced with success on patients with severe heart failure not controlled medical management. The dyspnea decreased and the patients could sleep whole night in the supine position, whereas before they had had to remain seated. ne physical capacity also increased, the patients being able to walk without difficulty. This improvement continued for six months after the tricuspid valvulotomy. The ligation of the inferior vena cava caused total disappearance of the rise of the venous pressure following the elevation of the lower limbs. The surgical treatment of the cardiac lung does not attempt to cure this condition definitely; it only attempts to lengthen the life with fewer limitations and without too much discomfort.

MORPHOLOGICAL EVIDENCE OF SPECIFIC INFLAMMATION IN THE BRAIN OF RHEUMATIC PATIENTS.—I. Costero, M.D., Mexico, D.F., Mexico.

The histologic changes which are always present in the brain of patients with active rheumatic fever are localized in the capillary vessels and in the microglial cells. Such changes will be described in detail.

In the brain of some children dying of active rheumatic fever, I have found certain nodules of ramifying microglia, which begin in miliary foci of necrobiosis localized most commonly in the gray matter of the pons. The Hortega cells of these nodules soon undergo clasmatodendrosis and give place to small areas of demyelinization, in which a few large neuroglia cells of the protoplasmatic type are found. The nodules are not necessarily related either to the blood vessels or to any of the other lesions, and they disappear within a short time without leaving a detectable connective-vascular scar.

It is possible that the nodules of ramifying microglia represent a hyperergic reaction similar to that responsible for the Aschoff nodule in connective tissue. They may, therefore, be useful for the histopathologic diagnosis of the encephalitic lesions during the evolutive period of rheumatic fever.

EXPERIMENTAL STUDIES ON THE VALIDITY OF THE CENTRAL TERMINAL OF WILSON AS AN INDIFFERENT REFERENCE POINT.—Martin Dolgin, M.D., Sidney Grau, M.D., and Louis N. Katz, M.D., Chicago, Ill.

To be published in full in the *American Heart Journal.*

COMMON SENSE MANAGEMENT OF AMBULATORY CORONARY ARTERY DISEASE.—Maurice A. Donovan, M.D., Schenectady, N. Y.

This paper discusses the genral management of ambulatory coronary disease in a series of eighty-nine patients observed over a two- to five-year period. It emphasizes the value of proper nitroglycerine therapy, the dietary management of obesity and high blood cholesterol, and a low sodium intake in associated hypertension. It emphasizes the worth of a proper psychosomatic evaluation in each patient. This necessitates a detailed personal history wherein the social, economic, and emotional problems of the individual are carefully considered. It often entails a painstaking investigation of the effect of their reactions upon the general attitude of the patient. When diagnosis has been obscure, a complete differential diagnostic workup has proved most valuable. It clearly shows the necessity for allotting ample time in each instance for frank discussion of the pathological problems involved. Some of these ambulatory patients have had former acute myocardial infarctions, but the majority fall into the clinical syndrome of coronary insufficiency.

THE RIGHT HEART CAVITIES, THE PULMONARY ARTERY AND THE INTERVENTRICULAR SEPTUM, FROM THE ANGIOCARDIOGRAPHIC VIEWPOINT.—Narno Dorbecker, M.D., and Jorge Deschampa, M.D., Mexico, D.F., Mexico.

The material used for this study has been selected from 265 angiocardiographic tracings made by the authors in the National Cardiological Institute of Mexico. Studies made preferably, but not exclusively, in cases of congenital heart disease, include: persistence of the ductus Botalli, interauricular septal defect, persistence of the common atrioventricular ostium, common arterial trunk, tetralogy of Fallot, complex of Eisenmenger, tricuspid atresia, and so forth.

The location, size, form of filling, time of emptying, interrelations, and distribution of the opaque substance have been studied, and the results compared with the data obtained from simple radiological studies. The similarities and differences shown in specific pathological states have been noted and the findings which may serve for differential diagnosis are pointed out. The position of the interventricular septum and the variations it undergoes in various abnormal states are indicated. The position, size, and relations of the pulmonary artery under abnormal conditions and its radiographic appearance in simple studies are demonstrated.

THE ELECTROCARDIOGRAM IN CASES OF VENTRICULAR ANEURYSM.—Maurice Eliaser, Jr., M.D., San Francisco, Calif.

The electrocardiographic changes in cases of ventricular aneurysm following myocardial infarction of the left ventricle have been reviewed. Records of previously published authentic cases and a personally observed series of fifteen instances have been classified. No pathognomonic electrocardiographic patterns have been detected, but two types of records have been observed to have occurred sufficiently frequently to be of clinical significance. In 37.7 per cent of cases the standard electrocardiograms reveal a downward directed major deflection in Lead 1, usually with inversion of the T wave and an upright P wave, with a positive ventricular complex in Lead III (QS_1 type). In 31.1 per cent of cases the ventricular complex in Leads II and III are directed downward with an upright major deflection in Lead I that may or may not be of low amplitude ($S_{2,3}$ type). In the remaining cases 13.3 per cent and 17.8 per cent reveal bundle branch block and nonspecific changes associated with myocardial infarction, respectively. Unipolar electrocardiography reveals that the QS_1 and $S_{2,3}$ types of record are caused by superimposition of rotational changes of the heart on patterns associated with myocardial infarction of the left ventricle. The initial position of the heart and the subsequent location of the aneurysmal sac are major factors in determining the ultimate configuration.

PRIMARY HEALED BACTERIAL VALVULAR ENDOCARDITIS WITH MULTIPLE MYOCARDIAL INFARCTS.—Norbert Enzer, M.D., Milwaukee, Wis.

This presentation is concerned with the detailed clinical and post-mortem records of a man who presented during life many of the features of subacute bacterial endocarditis. At no time during this illness was the diagnosis established by blood cultures. Post-mortem examination revealed the presence of a healed mitral endocarditis and multiple infarcts in the myocardium. In certain areas of the myocardium close to the endocardium, bacteria were identified in the sections. Nowhere in the tissues was there any evidence of rheumatic fever or other antecedent myocardial or endocardial disease. The diagnosis is further supported by the demonstration of renal lesions and multiple peripheral vascular lesions. The case further illustrates the importance of mural endocarditis which is active, while the valvular endocarditis is demonstrably healed.

THE FACTOR OF PULMONARY EMPHYSEMA AND RIGHT HEART STRAIN IN UNCOMPLICATED PULMONARY FIBROSIS (PNEUMOCONIOSIS).—Norbert Enzer, M.D., Milwaukee, Wis.

The pneumoconioses, especially silicosis, have attracted a great deal of attention and study in the past fifty years. These studies have been largely devoted toward a solution of the problems involved in the etiology and mechanism of the fibrosis. The high coincidence of tuberculosis stimulated research in that direction, too.

Only more recently has attention been directed to the effects of fibrosis on the nontuberculous lung. Investigations in this direction call for an appreciation of the pathogenesis and behavior of pulmonary emphysema, pulmanary arteriosclerosis, chronic bronchitis, bronchiolitis, fixation of the hilum, and the effect of all of these singly and combined on pulmonary ventilatian, pulmonary circulation, and the functions of the right heart. This complex has an important clinical aspect, for it is involved with the evaluation of these patients in terms of disability. Such disability sometimes is of great importance because of the Workmen's Compensation Law.

This presentation is concerned with the development of clinical, physiologic, and pathologic evidence aligned to throw some light upon the symptom complex of pulmonary fibrosis. Cases illustrating various phases will be used to highlight the thesis that, "Simple nodular, uninfected pulmonary fibrosis may be the cause of severe pulmonary emphysema, and that patients so affected are disabled because of this, and frequently die of right heart failure."

ORGANIC HEART DISEASE IN MALTA FEVER.—J. C. Etchevés, M.D., A. Cozza, M.D., and A. Alfonsín, M.D., Buenos Aires, Argentina.

Abstract in English not available.

THE ELECTROCARDIOGRAM IN PNEUMOPERITONEUM INCLUDING AUGMENTED UNIPOLAR LIMB LEADS AND UNIPOLAR CHEST AND ESOPHAGEAL LEADS.—Elwyn Evans, M.D., and Thomas C. Black, M.D., Orlando, Fla.

New terminology to facilitate description of the location of the chest electrode in positions other than C_1 through C_7, etc., was used. Positions starting one intercostal space above C_1 were labeled C', positions starting two intercostal spaces above were labelled C'', and those three intercostal spaces above, C'''. Those one intercostal space below were marked $C_{-'}$. Positions on the right were further identified by R.

Pneumoperitoneum changed all records in various degrees, but the changes were not always predictable. Esophageal tracings were taken on ten patients with pneumoperitoneum (four with left and three with right phreniphraxis). Three were taken with patients erect, seven erect and recumbent, and one during various phases of respiration. At ventricular levels, all showed abnormally large Q waves; nine showed abnormal T waves. Other constant findings were upward and probably forward displacement of the heart, noted roentgenographically.

It is concluded that heart position affects the electrocardiogram, including esophageal leads. Further, it is hazardous to diagnose old posterior myocardial infarction from the history when it is substantiated only by abnormal esophageal electrocardiograms.

CARDIAC OUTPUT IN ACUTE HYPOXEMIA.—M. Feldman, Jr., M.D., S. Rodbard, Ph.D., and L. N. Katz, M.D., Chicago, Ill.

This laboratory has recently been engaged in an analysis of the hemodynamic changes which occur after the induction of 100 per cent nitrogen breathing in anesthetized dogs. Immediately after the onset of nitrogen breathing, the blood flow nearly doubles in the superior vena cava, with a lesser increase in the inferior vena cava. Within seventy seconds a rise of blood pressure of 10 to 40 mm. Hg is observed. After the blood pressure begins to fall from its peak value, and when it has almost returned to its control value at about one hundred seconds, the flow in the inferior vena cava suddenly falls to nearly zero, although the flow in the superior vena cava also diminishes. With the resumption of air

breathing, there is a rapid return of flow in both the superior and inferior venae cavae, concomitant with a marked rise in blood pressure. After about three to four minutes the pressure and flow return to control values. The implications of these data are discussed.

BIOMETRIC PROFILE OF HYPERTENSIVE PATIENTS AT BOGOTA.—

Luis G. Forero Nougues, M.D., Bogota, Colombia.

At Bogota, Colombia, situated at an altitude of 2,615.215 meters above sea level, with a barometric pressure of 560,138 mm. Hg ± 0.834, three hundred forty-three hypertensive patients were studied biometrically according to the criteria of the New York Heart Association. Of these, 207 were women and 136 were men.

The findings were treated statistically with the following results:

Female Patients			Male Patients		
Weight	62.290 kg.	± 9.982	Weight	74.379 kg.	± 9.3882
Age	51.866 yr.	± 9.712	Age	53.755 yr.	± 8.6263
Electrical axis	+30°	± 4.599	Electrical axis	+30°	± 4.378
Height	155.50 cm.	± 5.254	Height	168.9 cm.	± 5.963
Vital capacity	2,269.0 c.c.	± 4.920	Vital capacity	3,168.4 c.c.	± 6.1068
Pulse	79.55 per min.	± 3.208	Pulse	74.20 per min.	± 3.386
Systolic blood pressure	17.30 cm. Hg	± 2.972	Systolic blood pressure	16.522 cm. Hg	± 2.7265
Nonprotein nitrogen	36.108 mg. %	± 1.519	Nonprotein nitrogen	38.821 mg. %	± 1.732
Distance between midsternal line and heart apex	97.049 mm.	± 1.753	Distance between midsternal line and heart apex	107.62 cm.	± 1.900
Diastolic blood pressure	9.827 cm. Hg	± 1.586	Diastolic blood pressure	9.7613 cm. Hg	± 1.6751
Respiration	20.18 per min.	± 1.41	Respiration	20.238 per min.	± 1.536
Surface area	1.607 sq. M.	± 0.884	Surface area	1.810 sq. M.	± 0.7964
Intercostal space	5.366	± 0.7312	Intercostal space	5.395	± 0.7174
Optic fundus	1.652 (K-W grouping)	± 0.715	Optic fundus	1.7594 (K-W grouping)	± 0.7947

RÉSUMÉ OF PRESENT CONCEPTIONS OF HYPERTENSION.—

Salvador García Tellez, M.D., Mexico, D.F., Mexico.

Abstract in English not available.

BIOSYNTHESIS OF RADIOACTIVE DIGITOXIN USING CARBON 14.—

E. M. K. Geiling, M.D., F. E. Kelsey, M.D., and B. J. McIntosh, M.D., Chicago, Ill.

The availability of carbon 14 now makes possible the preparation of a large number of important drugs with reasonable amounts of radioactivity incorporated in the molecule either by direct chemical synthesis or by biosynthesis. We have prepared radioactive digitoxin from the dried leaves of Digitalis purpurea grown in the laboratory.

Suitable young plants were transplanted into quartz sand and maintained with an inorganic nutrient solution. Each plant was sealed in two battery jars placed with the open ends in apposition. Carbon 14 was introduced as carbon dioxide. The sealed plants grew well and were harvested after about thirty days of exposure to C14.

Radioactive digitoxin was extracted from the dried leaves with 50 per cent alcohol. The extract was purified by precipitation with lead acetate; the digitoxin was removed with choloroform and precipitated from dilute alcohol solution. Determination of radioactivity was made by using nonradioactive digitoxin as a carrier, with a mica-window Geiger counter.

The activity of the preparation is such that approximately 5 per cent of the total dose in animals can be detected with accuracy. Tissue distribution studies in isolated heart preparations as well as in small laboratory animals are now under way.

IMPORTANCE OF PSYCHIC COMPONENTS OF PAIN IN THE COURSE OF CORONARY DISEASES.—R. GODEL, M.D., ISMAILIA, EGYPT.

In coronary diseases, whether the latter causes transitory myocardial ischemia or subacute infarction, pain of purely psychic origin frequently adds its component to the syndrome. Should such pain be severe, occur repeatedly, and be associated with anxiety, then the clinical picture becomes greatly confused. The origin of each single crisis is erroneously traced back to coronary insufficiency; prolonged bed rest is enforced upon the patient who becomes ever more heart-conscious, distressed, and emotionally fixed upon his ailment.

However, before the psychic components of the pain are searched for, the patient should undergo thorough cardiological investigation. The type of coronary disease which affects him is determined: chronic nonprogressive form, progressive type, or protracted coronary insufficiency. This task rests upon careful interpretation of clinical signs and symptoms, serial electrocardiograms, blood sedimentation figures, and leucocyte counts. Psychic components are then analyzed and their relative importance estimated. The patient should be encouraged and helped to work out his emotional problems. These may have centered upon sexual, competitive, aggressive forces, and upon relationships of a more or less regressive type. Narcoanalysis can help in liberating repressed complexes and conditionings. Elimination or attenuation of disturbing psychic material will considerably reduce the frequency of cardiac pain. It will also help clarify the clinical picture.

AN OPTIMAL SYSTEM FOR THE TREATMENT OF THE FAILING HEART.—HARRY GOLD, M.D., NEW YORK, N. Y.

The conclusions of extensive experience are presented.

A SIMPLE METHOD OF DETERMINING ABNORMALITIES OF THE Q-T INTERVAL AND ITS VALUE IN ACUTE RHEUMATIC FEVER.—EMANUEL GOLDBERGER, M.D., AND MURRAY J. POKRESS, M.D., NEW YORK, N. Y.

To be published in full in *American Heart Journal*.

CONTRIBUTION TO THE STUDY OF ERYTHROBLASTEMIA IN CARDIAC PATIENTS.—I. GONZALEZ GUZMAN, M.D., MEXICO, D.F., MEXICO.

Studying several thousands of cytohematic examinations made at the National Institute of Cardiology of Mexico, we found some showing a significant percentage of erythroblasts in the blood. The analysis of the corresponding clinical data revealed some important facts, which can be summarized as follows:

1. Anemia of about 2.0 million red cells per cubic millimeter generally shows some circulating erythroblasts. This erythroblastemia is always slight; it is not constant and has no relation to the number of red cells.
2. When anemia appears together with cardiac failure, the erythroblastemia is more frequent and important; it is not related to the anemia, but to the degree of cardiac failure.
3. In cases of marked heart failure erythroblasts appear in the blood sometimes in high percentages even when the number of red cells is normal or above normal.
4. The nucleated red corpuscles present in cases of heart failure are all normoblastic, seldom basophilic, and almost always polychromatic and orthochromatic.
5. In cases of cardiac failure with pulmonary infarct, bronchopneumonic foci, or pneumonia, binucleated normoblasts, paraerythroblasts of Lehndorff, appear in the circulation.

6. The significance of paraerythroblasts is discussed and some experiments on their origin are outlined. The clinical and experimental data lead us to conclude that the normoblastic nuclei suffer a deformation and the normoblasts take on a binucleated appearance because of colloidal conflicts of the antigen-antibody type which take place in the interior of nucleated corpuscles. The antigens are degraded proteins liberated in tissues in which an extravasation of red corpuscles occurs. The antibodies are elaborated by the organism as a response to the degraded proteins which are set free from the red cells when they are destroyed in a tissue rich in reticuloendothelial cells.

7. The cause of erythroblastemia is anoxia of the bone marrow.

PATTERN Q_1-Q_2-Q_3. ROTATION AND DISPLACEMENT OVER THE THREE EXPERIMENTAL AXES.—Antonio Gómez Hernández, M.D., Havana, Cuba.

The technique for rotating and displacing the heart on its three axes to extreme positions is described. It is confirmed that by clockwise rotation of the heart, the S_1 Q_3 pattern is always obtained, and by counterclockwise rotation, Q_1 S_3 is produced. Likewise, convergent tracings are produced in V_L and V_F by making the heart vertical, that is, moving the apex to the right. On the other hand, divergent tracings are produced by making the heart horizontal by moving the apex to the left. On backward projection of the apex the pattern S_1 S_2 S_3 described by Ashman is produced. This does not occur when the apex is moved forward. It is necessary to rotate the heart a little clockwise in order to cause the initial negative element Q to be produced without exception. Five cases are shown of the Q_1 Q_2 Q_3 pattern, two of them with amplitudes and widths above the values considered as normal. Aside from this, we were not able to obtain in these cases clinical or radiographical evidence of cardiovascular pathology.

MERCURIAL DIURETICS. A NEW THERAPEUTIC APPROACH WHEN INTOLERANCE OR HYPERSENSITIVITY EXISTS.—Luis González Sabathié, M.D., V. S. Terán, M.D., and O. Robiolo, M.D., Rosario, Argentina.

Abstract in English not available.

PAROXYSMAL TACHYCARDIA OF INFANTS UNDER ONE YEAR.—Luis González Sabathié, M.D., and Osvaldo Robiolo, M.D., Rosario, Argentina.

Eight observations of paroxysmal tachycardia of infants under one year are reported. These, in addition to the forty-three observations found in the literature, bring the number of reports on this rare clinical phenomenon to fifty-one. These cases were studied between 1938 and 1946, five of the cases having occurred in the same year. All were of the supraventricular type. Six cases ended in recovery, two in death.

The clinical picture is described in detail. Symptomatology, duration of the ιacks, their repetition, maternal antecedents, existence of etiological factors, ediate and later evolution, type of tachycardia, and noticed frequency are lyzed. The electrocardiograms are analyzed, and the modifications after the d of the attack pointed out. They appear as a true post-tachycardial syndrome caused to a large extent by the use of quinidine.

For the cases observed during pregnancy, it is proposed to use the term "Prenatal Paroxysmal Tachycardia," instead of "Congenital Paroxysmal Tachycardia."

The therapeutic remedies used to date are discussed, and the form is described in which quinidine sulfate has been used orally with good results and without untoward effects.

The mechanical procedure of vagal stimulation gave good results in two cases observed.

CALCIFICATION OF THE MYOCARDIUM.—Luis González Sabathié, M.D., and M. Voogl, M.D., Rosario, Argentina.

Abstract in English not available.

NEWER CONCEPTS CONCERNING THE SYNDROME OF SHORT P-R INTERVAL AND WIDE QRS COMPLEX.—Juan Govea Peña, M.D., Havana, Cuba.

Abstract in English not available.

CARDIAC LESIONS IN RHEUMATOID ARTHRITIS.—Irving Graef, M.D., Daniel V. Hickey, M.D., and Vladimir Altmann, M.D., New York, N. Y.

The protocols and available microscopic sections of the heart were reviewed for cardiac lesions in sixty-six cases of rheumatoid arthritis studied at necropsy between 1939 and 1948 at the Goldwater Memorial Hospital, Welfare Island, New York City.

There were thirty men and thirty-six women distributed according to age between the third and ninth decades. The mean age for both groups was in the seventh decade; the mode of their distribution fell in the sixth and seventh decades. Antecedent rheumatic fever was reported in the history of one patient.

Gross valvular deformities were observed in twenty-nine cases; of these, nineteen were regarded as of the rheumatic type, but mild. In only one was there mitral stenosis. In five additional cases microscopic examination disclosed old rheumatic valvulitis. In two there were granulomatous zones of interstitial collagenous necrosis undistinguished from those seen in rheumatoid subcutaneous nodules.

Pericarditis consisting usually of old adhesive or obliterative lesions was found in one-half of the cases. In four, clinically unsuspected acute fibrinous pericarditis was found. In one a group of necrotic collagenous nodules with a granulomatous reaction like those seen in subcutaneous nodes was seen in histologic preparations.

Myocardial lesions included seven instances with active chronic inflammatory interstitial myocarditis. Among these there were five of the granulomatous type which resembled Aschoff nodules. In addition, perivascular fibrosis of significant degree and characteristically arranged in "onionskin" layers was found in about two-fifths of the cases. In two cases lesions like those of periarteritis nodosa were found in the coronary arteries, although periarteritis nodosa was unsuspected ante mortem.

On the basis of these results there were twenty-six cases with definite rheumatic types of cardiac lesions and nine others which were probably rheumatic, but in them the evidence was not conclusive. These data indicate that careful study of the heart in rheumatoid arthritis is warranted, even in the absence of overt clinical or gross pathologic deformities. The evidence of cardiac involvement resembles that seen in rheumatic fever, but is less diffuse or severe, as a rule.

A COMPARISON OF PRECORDIAL ELECTROCARDIOGRAMS OBTAINED WITH CR, CL, CF, AND V LEADS.—Sidney Grau, M.D., Martin Dolgin, M.D., and Louis N. Katz, M.D., Chicago, Ill.

Published in full, Am. Heart J. **37:** 343, 1949.

THE VALUE OF DIET IN THE MANAGEMENT OF HYPERTENSION.—IRVING GREENFIELD, M.D., WOODMERE, N. Y.

Twenty patients in the fifth and sixth decades, with long-standing hypertension, have been observed. Therapy consisted of a low-sodium diet modeled after the Kempner regime. Control studies included history, physical examination, teleroentgenograms, electrocardiograms, blood count, blood chemistry, and urinalysis. These patients were observed as ambulatory patients and studies were limited to those procedures which could be carried out in the management of the ambulatory patient seen in the office of the physician. The beneficial effects seen in the teleroentgenogram, electrocardiogram, and blood pressure will be presented. The reversibility of hypertensive cardiac disease will be demonstrated. In a small group of these patients, the beneficial effects of this regime were obtained, but during the course of management, dietary indiscretions were committed; data will be presented to show the unfavorable effects of these dietary indiscretions as well as the reversibility of these changes with resumption of diet. In the decompensated patient with hypertensive cardiovascular disease, the beneficial effects of this regime on water retention with resulting diminution in the required maintenance dose of digitalis will be noted.

THE ETIOLOGY OF PERICARDITIS.—GEORGE C. GRIFFITH, M.D., AND LEON WALLACE, M.D., LOS ANGELES, CALIF.

Approximately fifty years ago Preble analyzed the etiological factors in 244 cases of pericarditis. With more effective methods of treatment, the etiological factors should be altered and the incidence of certain causative agents lowered.

Source of Material.—A survey of 13,353 consecutive autopsies performed in the Los Angeles County Hospital during the seven years 1940 through 1946 was carefully reviewed with reference to the etiology of pericarditis.

Analysis of Data.—Seven hundred twenty-nine cases of pericarditis were found. This is a total incidence of 5.4 per cent.

Comment.—The general incidence of pericarditis is slightly higher than that reported by Smith and Willius in 1932. They reported an incidence of 4.2 per cent in 8,912 necropsies. Of the acute inflammatory types of pericarditis, nonspecific idiopathic pericarditis shows the highest incidence. If rheumatic pericarditis is added to the idiopathic pericarditis, the percentage equals the percentage incidence of rheumatic pericarditis reported fifty years ago by Preble. Tuberculous and pneumonic pericarditis have definitely decreased in frequency. Uremic pericarditis and pericarditis from acute and chronic coronary artery disease have definitely increased in frequency. Metastatic malignant disease involving the pericardium remains about the same each year.

The following conclusions are drawn: (1) The general incidence of pericarditis is 5.4 per cent. (2) Tuberculous and pneumonic pericarditis have definitely lessened. (3) Pericarditis of idiopathic and rheumatic origin is high in frequency. (4) The incidence of pericarditis secondary to uremia, coronary artery disease, and malignant diseases is definitely increased.

TOMOGRAPHIC STUDY OF THE CONGENITAL DILATATION OF THE PULMONARY ARTERY.—ADAMO GRILLI, M.D., AND VITTORIO PUDDU, M.D., ROME, ITALY.

Tomographic studies on four female patients (from 36 to 50 years of age) gave a clear picture of the dilatation of the pulmonary artery and its branches and allowed localization of the lesion. Two patients showed a bilateral dilatation: one of these had an enlarged heart with a contour similar to that of the classical picture of interauricular septal defect. The other two patients had a unilateral or predominant dilatation of the left branch; the heart was little enlarged in both cases.

THE ANALYSIS OF THE CARDIOGRAM OBTAINED WITH IMPROVED TECHNIQUE.—Franz M. Groedel, M.D., New York, N. Y.

The cardiogram, the record of the cardiac concussion of the chest wall, in older times highly valued, is hardly mentioned in modern literature. Technical difficulties discouraged physicians from continuing the use of this clinical method. The technique of electrical pulse recording with special microphones, conceived by the author, facilitated cardiography greatly. The special receiver bell, developed for phlebography, was fastened to the chest and varied determinable pressure was exerted on the bell. Analysis of cardiogram and phlebogram, with the aid of simultaneously recorded cardiophonograms and electrocardiograms, was routinely exercised for several years.

Results.—The conception that the cardiogram records only the ventricular movements must be discarded. The cardiogram, when recorded with this sensitive method—just like the phlebogram—mirrors every mechanical cardiac event occurring during one heart cycle and, frequently, is even more differentiated than the phlebogram. The isometric and isotonic contraction of each ventricle, the various systolic phases, the opening and closing of each valve, the movements of each auricle, the mechanical event causing the third sound, are reflected in most cardiograms. Characteristic differences in configuration exist over the various chest areas and between the normal and diseased heart.

THE USE OF A SPOT FILM RADIOGRAPHIC DEVICE IN CARDIAC ROENTGENOLOGY.—Nathan Grossman, M.D., Milwaukee, Wis.

Radiological examination of the heart calls for identification of the several chambers and segments of these chambers in the various views, namely, the posteroanterior, the left anterior oblique, and the right anterior oblique. Correlation with the clinical picture gives the cardiologist an idea of the status of the myocardium from a dynamic standpoint. Examination of the various segments of these several chambers requires positioning of the patient with specific reference to each individual chamber in that the same oblique position is not satisfactory for the examination of chambers whose silhouette is present in a given view. Because of the requirements of line positioning, fluoroscopy has its greatest use. The disadvantage of this method is that no pemanent record for comparison or study is retained. It is suggested that the use of spot films of the various chambers and segments of these chambers be made in order to overcome the difficulty described. This would eliminate the personal equation to some extent and certainly would afford opportunities for subsequent comparison.

Technique and technical factors are described. Several illustrations are included. Advantages and disadvantages of the method are enumerated.

DYNAMICS OF THE INTERVENTRICULAR SEPTUM.—Richard Gubner, M.D., Harry E. Ungerleider, M.D., and Irving Hirshleifer, M.D., New York, N. Y.

The dynamic role of the interventricular septum has been largely overlooked because of its inaccessibility to study. The presence of large ventricular type pulsations along the right heart border in aortic insufficiency can be interpreted only as evidence of a powerful movement of the septum to the left in systole carrying the right side of the heart with it. More direct observation of the movement of the interventricular septum has been accomplished by roentgenkymographic study in the left anterior oblique position during contrast visualization of the heart chambers with Diodrast. With this technique whereby the septum is visualized, it is found that the excursion of the interventricular septum considerably exceeds that of the free left ventricular wall. It is evident that the

interventricular septum has a most important function in left ventricular contraction. The nature of the septal movement makes dubious the existence of the so-called Bernheim syndrome. The contrast roentgenkymographic technique yields much additional information, namely, the thickness of the left ventricular wall and the extent of systolic emptying of the ventricular cavity. It also permits study of cyclic blood flow changes in the auricles and great vessels.

EFFECTS OF IONS AND DRUGS UPON MYOCARDIAL RHYTHMS INDUCED AT THE ANODE AND CATHODE APPLIED TO THE MAMMALIAN VENTRICLE.—A. SIDNEY HARRIS, M.D., HOUSTON, TEXAS.

Characteristics of the response of cardiac muscle at the anode and the cathode during the passage of direct currents have been reported. The modifications in those electrically induced reactions brought about by ions and drugs are being recorded to reveal (a) common properties as shown by ectopic thresholds and patterns and (b) factors that predispose to ventricular fibrillation or prevent it.

In dogs anesthetized with morphine and a minimal dose of barbital sodium (180 mg. per kilogram), the cathodal response is regular ectopic tachycardia. The anodal response is short accelerating paroxysms which often lead quickly into ventricular fibrillation. Regular tachycardia seldom produces fibrillation.

The local application of drops of 1:1000 epinephrine hydrochloride at the stigmatic slightly lowers the cathodal threshold, the rhythm remaining regular. The anodal threshold is increased, and the tendency to accelerating responses is maintained or enhanced. The probability of fibrillation upon effective anodal stimulation is greater.

Drops of 5 per cent calcium chloride raise cathodal and anodal thresholds, the cathodal changing more. The cathodal rhythm usually remains regular. The anodal rhythm is changed by calcium ions from the accelerating type to a regular one. The probability of fibrillation is greatly diminished.

In dogs anesthetized with pentobarbital sodium, near-threshold cathodal stimulation often produces a coupled or bigeminal rhythm, considered indicative of recovery through supernormality. Anodal stimulation produces a regular and not accelerating rhythm. The probability of fibrillation is low.

In all tests the tendency to an accelerating rhythm upon anodal stimulation was associated with high probability of fibrillation, and a change to regular rhythm reduced this probability.

EXPERIMENTAL HYPERVOLEMIC HEART FAILURE.—TINSLEY R. HARRISON, M.D., DALLAS, TEXAS.

Cardiac overload has been produced in dogs by the intravenous administration of large volumes of albumin solution or of blood. The point at which the cardiac output fails to continue increasing or begins to decline, despite the continued further rise in venous pressure, has been taken as the point indicating the onset of heart failure. The comparison of these results with those found in the ordinary types of clinical heart failure would indicate one of two possible conclusions: (a) Either one must conclude that there are multiple types of heart failure with multiple fundamental hemodynamic disturbances, or (b) if a single hemodynamic defect exists in all types of heart failure, this is a defective response in relation to filling load. The latter assumption is in keeping with the classical physiological and clinical concepts. If this assumption is correct, such factors as inadequate tissue blood supply, diminished renal blood flow, and so forth, are to be regarded as secondary, although at times very important factors.

RHEUMATIC FEVER IN HAWAII.—Alfred S. Hartwell, M.D., Honolulu, T. H., Hawaii.

A brief summary of the geographic location, temperature, and rainfall of Hawaii is given. The variegated population and racial percentages are shown. Until ten years ago rheumatic fever was thought not to exist in Hawaii. Recently interest has increased. A five-year study of hospital admissions for heart disease in Honolulu is described. A total of 1,269 cases were studied: 218 (17.1 per cent) had rheumatic heart disease or rheumatic fever. There were 330 admissions among these patients, or 0.4 per cent of 81,949 patients admitted to the medical services of four hospitals.

Fifty-one of the rheumatic patients died, a mortality of 23.4 per cent. Sex, age, and racial origin are discussed. One hundred sixty-three (74.7 per cent) were born and lived in Hawaii. Those with cardiac involvement (89.9 per cent), the valves involved, the incidence or pericarditis (9.1 per cent), auricular fibrillation (16.1 per cent), chorea (2.3 per cent), congestive failure (18.2 per cent), and active carditis (35.3 per cent) are shown.

Rheumatic fever in Hawaii is a mild disease, rarely showing acute arthritis or high fever.

ON CHANGES OF THE T WAVE AND THE RS-T SEGMENT OF THE HUMAN ELECTROCARDIOGRAM.—Hans H. Hecht, M.D., Salt Lake City, Utah.

The electrical behavior of isolated nerve and muscle cells, the results obtained from animal experiments, and induced alterations of the human endo- and epicardial electrocardiogram suggest that the majority, if not all, of the RS-T segment shifts and T-wave changes are governed by four basic factors: (1) Slowing the rate of repolarization (lengthening the duration of the activated state) of subepicardial regions results in inversion of the terminal portion of T in epicardial leads or in leads to which the electrical effects of epicardial regions are being deflected ("ischemia"). (2) Similar processes occurring endocardially manifest themselves in epicardial leads by increasing the height of T or by uprighting a previously inverted T wave ("paradoxical reversal"). (3) Lesions of greater intensity result in incomplete repolarization of the region injured and in flow of electrical currents at rest ("injury"). Subepicardial lesions are characterized by an apparent elevation of the RS-T segment in epicardial leads while (4) depression of RS-T in such leads signals intense alterations of the endocardial surface.

A number of procedures known to alter the rate of repolarization which were carried out in subjects with normal and abnormal resting electrocardiograms demonstrate that these concepts are applicable to the human heart. It may be shown that spontaneous RS-T segment shifts and T-wave changes may be viewed as combinations and mixtures of endocardial and epicardial "repolarization delay" (ischemia) and endocardial and epicardial "resting currents" (injury). A rational interpretation of T-wave changes in general appears feasible on this basis.

ELECTROCARDIOGRAPHIC CHANGES FOLLOWING ELECTROSHOCK THERAPY IN CURARIZED PATIENTS.—Milton R. Hejtmancik, M.D., Alexander J. Bankhead, M.D., and George H. Herrmann, M.D., Galveston, Texas.

To be published in full in *American Heart Journal.*

STUDIES ON THE PROPAGATION OF THE PULSE INTO THE MINUTE SKIN ARTERIES.—ALRICK B. HERTZMAN, M.D., ST. LOUIS, MO.

Under normal conditions, the contour of the skin pulse as recorded photoelectrically resembles closely that of the pulse in the parent arteries. (Compare the finger pad pulses with those in the digital and radial arteries.) Changes in the contour of the skin pulse depend less on the resistance in the minute arteries than on the ratio of the resistances in these and the parent arteries. Thus, dicrotism in the skin pulses results from the dilatations due to heat and Mecholyl but not from that induced by histamine, although the increase in blood flow from the two drugs is approximately equal. Again, during the early phase of the reactive dilatation from cold the pulses of the finger pad are extremly rounded until the digital artery begins to dilate. Similar but less marked rounding of the skin pulse occurs in hypertension and in peripheral arterial diseases. These changes in contour can be induced in normal subjects by compression of the digital artery with Gartner's capsules of varying length and inflated to various pressures. The use of these changes in contour in the location of sites of resistance to flow will be discussed.

ON HEART SYNAPTIC BLOCKING SUBSTANCES.—C. HEYMANS, M.D., GHENT, BELGIUM.

Several substances, including nicotine, acetylcholine, eserine, and Prostigmine, may block the conduction of the heart synapses, generally after a primary period of synaptic stimulation. Several drugs have been tested in order to investigate their action on synaptic transmission and excitability in the heart. These experimental investigations performed in dogs showed:

1. Di-isopropyl fluorophosphate (DFP) first stimulates the vagus synapses and may block further the vagal synaptic transmission and excitability. These effects are not related to the anticholinesterase influences of DFP.

2. Diethylamino-ethyl ester of phenyl-cyclopentane carbonic acid blocks the vagal and sympathetic synaptic transmission and excitability, without affecting the postsynaptic elements. Vagal stimulation, nicotine and DFP then have no effect on the heart rate, but acetylcholine still induces bradycardia. Higher doses also paralyze the postsynaptic vagal innervation and suppress the acetylcholine bradycardia.

3. Tubocurarine and the synthetic curarizing substances, di-iodo-ethyl of bis (quinoline-oxy-8')-1-5 pentane and tri-iodo-tri (triethyl-ammonium-methoxy) 1-2-3 benzene, in given doses, paralyze the cardiac vagal synapses.

4. Tetra-ethyl ammonium paralyzes the cardiac vagal, but not the cardiac sympathetic synapses. After this, neither vagal stimulation, nor nicotine, nor DFP will slow the heart, but acetylcholine still induces bradycardia.

5. Dibenzyl-dichlorothylamine (Dibenamine) does not paralyze the vagal synapses of the heart.

THE SYRACUSE AREA RHEUMATIC FEVER PROGRAM.—J. G. FRED HISS, M.D., SYRACUSE, N. Y.

A description of rheumatic fever program as developed in the Syracuse area will be presented. The sponsoring organization (The Rheumatic Fever Foundation) was chartered by the State of New York, Oct. 26, 1945, and is supported by membership dues and voluntary contributions. The program is organized in six basic parts, as follows: (1) program of professional and lay education, (2) diagnostic clinic, (3) special rheumatic fever hospital, (4) follow-up clinic, (5) case-finding program, and (6) research.

THE EFFECT OF A LOW FAT DIET ON THE SPONTANEOUSLY OCCURRING ARTERIOSCLEROSIS OF THE CHICKEN.—Louis Horlick, M.D., and Louis N. Katz, M.D., Chicago, Ill.

To be published in full in *American Heart Journal.*

SPLANCHNICECTOMY IN RELATION TO HYPERTENSIVE DISEASE OF PREGNANCY.—Emil M. Isberg, M.D., and Max M. Peet, M.D., Ann Arbor, Mich.

The large number of hypertensive women who were treated by splanchnicectomy at the University of Michigan Hospital presented the opportunity to investigate several aspects of the incompletely understood entity of hypertensive disease of pregnancy, especially in its relation to the autonomic nervous system and the operation of bilateral supradiaphragmatic splanchnicectomy.

The findings of this study strongly suggest that the surgical procedure of splanchnicectomy is worthy of being utilized in the management of some of the problems of hypertensive disease of pregnancy for the following reasons:

1. Not a single one of eighteen hypertensive women who responded to splanchnicectomy by maintaining normal blood pressure levels after operation and who subsequently became pregnant developed a toxemia of pregnancy.

2. Two cases of toxemia superimposed upon prepregnant hypertension and operated upon during pregnancy responded dramatically to splanchnicectomy, with prompt disappearance of the toxemias and the achievement of normal blood pressure levels for the remainder of the pregnancies and during a long postpartum follow-up period.

3. Women whose hypertension was first recognized during pregnancy manifested a better response to splanchnicectomy than did women whose hypertensive disease bore no relation to pregnancy, even though the clinical pictures of the two groups are alike prior to operation.

HEART DISEASE OF PREGNANCY.—Julius Jensen, M.D., St. Louis, Mo.

The paper considers the pathological effects of pregnancy on the cardiovascular system. Evidence has been accumulated in the literature recently that pregnancy, as such, may have effects on the myocardium which lead to the development of definite pathological changes in the heart muscle and, clinically, to congestive heart failure, which may occur during pregnancy, with or without association with hypertension, and also post partum. It is possible that this process is related to changes in the blood pressure and in the electrocardiogram which are sometimes seen associated with childbearing.

Several personal experiences, including electrocardiographic observations, form the original contribution to this subject.

ACTIVE PARTICIPATION OF THE ARTERIAL WALL IN ARTERIAL PRESSURE ADJUSTMENT.—C. Jiménez-Díaz, M.D., P. Barreda, M.D., and A. F. Molina, M.D., Madrid, Spain.

Stimulation of the central end of the vagi is used as a test to produce sharp arterial hypertension in the anesthetized dog. This effect is not suppressed even when the pituitary gland, the kidneys, and the adrenals are removed. Conversely, it disappears when the cervical spinal cord is sectioned. It is, therefore, the result of a reflex whose afferent path is the sensitive vagus, and whose efferent path is the sympathetic nerves. The humoral nature of the sympathetic action on the arterial wall is shown in crossed-circulation experiments, with simultaneous hypertension *in the receptor dog* when the vagi are stimulated in the

donor; and also by the fact that in the plasma of the dog there are present during the hypertension substances with vasoconstrictor action on the Lewen-Trendelenburg preparation of the frog.

In the experimental animal in which the upper and lower halves of the body have been separated, except for the nervous system, the former fed by the heart and the latter by pump perfusion, hypertension was produced also in the lower half by stimulation of the vagus, simultaneously with the increase of blood pressure in the upper half. But this only takes place if the lower half is perfused with dog plasma; if it is perfused with normal saline, the blood pressure does not increase.

It may be concluded from these experiences that the nervous action on the arterial wall frees something which acts on the plasma to produce the hypertensive substance. Through analogy with the system from the ischemic kidney it is admitted that the material from the artery is a ferment, "arterin," that acts upon the hypertensinogen of the plasma to produce the "arteriohypertensin," a fundamental factor in the regulation of pressure and tone of arteries. Arterial extracts that have no hypertensive action acquire it when incubated together with plasma "hypertonogen" of the same animal. This effect is very similar to the renal hypertensin and is also potentiated by cocaine. The meaning of this humoral-enzymatic mechanism regulating blood pressure is discussed.

SUBACUTE ABACTERIAL ENDOCARDITIS.—C. Jiménez-Díaz, M.D., E. Arjona, M.D., and E. Lopez-Garcia, M.D., Madrid, Spain,

The authors have described their observations on patients with a clinical picture quite similar to that of bacterial endocarditis, with a febrile course and a malignant evolution, in which blood cultures are persistently negative. This is called "subacute abacterial endocarditis."

The clinical picture has been based upon forty-one detailed cases, analyzing the differences and similarities to bacterial endocarditis. A presumptive differential diagnosis is clinically possible, strengthened by negative blood cultures. The pathological study stresses the distinctive character of this kind of endocarditis, first described by these authors. Cultures of the cardiac valves and of other organs have also always been negative. Certain differential characteristics are also found in the histological study.

The relationship between Libman's bacteria-free stage and the indeterminate endocarditis of Gross and Friedberg is discussed, and it is concluded that an active infection by an organism that cannot be isolated with current techniques is being dealt with (malignant rheumatic fever, associated virus, or rickettsia?).

Attention is drawn to penicillin resistance which requires very high doses to obtain beneficial results.

CARDIOVASCULAR EPILEPSY.—Fuad Kandalla, M.D., Bagdad, Iraq.

Atypical cardiovascular emergencies intractable to known cardiac drugs may be due to atypical epilepsy. The diencephalon controls the cardiovascular system as well as the central nervous system. Diencephalic epilepsy may simulate -diovascular arrhythmias. In such a case, intravenous injection of sodium barbital might be a life-saving measure, replacing digitalis, ouabain, mer- diuretics, quinidine, or even adrenalin. This does not mean that one give first choice to anticonvulsant drugs, but rather that they should be considered in case of unexpected failure of cardiotonic drugs.

Cardiovascular epilepsy may be genetic (complete or incomplete) or agenetic (complete or incomplete). Clinical types consist of (1) vasomotor anginal epilepsy, (2) paroxysmal tachycardial epilepsy, and (3) hypertensive encephalo-

pathic epilepsy. A migrainoid type is also described. Agenetic epilepsy (latent) is precipitated by nervous tension or coronary vasomotor constriction.

The chief symptom is cardiac pain without effort and without demonstrable organic cardiac disease. There is a definite familial history of epilepsy. The treatment is the use of barbiturates. If diabetes, nephritis, arteriosclerosis, cardiac enlargement, or other diseases are present, these should be treated.

CHRONIC COR PULMONALE DUE TO BILHARZIAL PULMONARY OBLITERATIVE ARTERIOLITIS.—M. R. Kenawy, M.D., Cairo, Egypt.

To be published in full in the *American Heart Journal.*

THE CORONARY VASODILATOR ACTION OF KHELLIN.—G. V. Anrep, M.D., M. R., Kenawy, M.D., and G. S. Barsoum, M.D., Cairo, Egypt.

Published in full in this issue.

TRANSMISSION OF SOUNDS IN CARDIOVASCULAR DISEASE.—William J. Kerr, M.D., San Francisco, Calif.

Demonstration by lantern slides of murmurs in aortic stenosis and two of the commoner congenital lesions, patent ductus arteriosus and coarctation of the aorta, shows the value of time relationships to the ventricular systole in diagnosing these clinical conditions. The use of techniques at the bedside will be discussed whereby differentiation can be achieved. The symballophone, a modified and double stethoscope, permits comparison of sounds and determination of time relationships essential to the examination.

NEW APPLICATIONS OF CHEST LEAD DIAGRAMS AND CIRCUMFERENTIAL LEADS IN CLINICAL CARDIOLOGY.—Bruno Kisch, M.D., New York, N. Y.

The author has previously described the use of chest lead diagrams for the graphic registration of electrocardiographic changes in circumferential leads. In 200 not yet published complete chest explorations in human beings, done in collaboration with Dr. B. Richman, and in not yet published animal experiments, the following findings were obtained.

The chest lead diagram shows, as a rule, a typical configuration in cases with left axis deviation due to hypertrophy of the left ventricle which is different from that due to positional change of the heart. New data confirm the previous statement that in posterior wall infarction a QS pattern is found, as a rule, on the right side of the chest chiefly or exclusively in CL leads. In patients with hypertensive patterns in the standard leads (high voltage and widening of QRS, depressed RS-T segment in Lead I, and inverted T_1), a QS pattern is also found on the right side of the chest but chiefly or exclusively in CF leads.

The studies of recent material again support the opinion that in cases of right axis deviation and in right ventricular hypertrophy the high R or R′ on the right side (mainly present in CL), which decreases the nearer the electrode approaches the sternum, is produced by the left ventricle. The first R in cases with R′ is the R of the right ventricle.

The statement made many years ago and since confirmed by other authors that whenever depression of the RS-T segment appears anywhere in the chest leads in man or in animal experiments, or in direct leads, an opposite place on the heart or chest can be found with elevation of the RS-T segment is proved again. This can be applied to cases of coronary thrombosis as well as coronary insufficiency and proves helpful in the localization of the damaged area.

ON THE MEASUREMENT OF THE QRS COMPLEX AND THE INTERPRETATION THEREOF BY DIRECT AND INDIRECT DEDUCTION.—J. B. KLEYN, M.D., AND R. M. F. HOUTAPPEL, THE HAGUE, HOLLAND.

To be published in full in *American Heart Journal.*

VARIABILITY OF ENDOCARDIAL POTENTIALS OF THE RIGHT VENTRICLE.—CHARLES E. KOSSMANN, M.D., ADOLPH R. BERGER, M.D., J. BRUMLIK, M.D., STANLEY BRILLER, M.D., and BERTHA RADER, M.D., NEW YORK, N. Y.

In the course of a series of experiments concerned with the determination of the action potentials developed in the interior of the heart in man, it was noted that the nature of the deflections obtained, particularly in abnormal hearts, depended upon the location of the electrode in the cavity of the right ventricle. This was particularly true when standard and precordial leads suggested block of the right bundle branch. In order to support the accuracy of this belief, the following procedure was instituted in several patients:

The electrode was introduced into the pulmonary artery. Then with the potential being recorded from the interior simultaneously with a fixed lead from the exterior (usually standard Lead I), a continuous record was made as the electrode was slowly withdrawn from the pulmonary artery into the right ventricle, then into the right atrium, and finally into the superior vena cava. By this technique an exploration was made of the right side of the interventricular septum, usually from the upper end of the outflow tract, down to the apex, and then along the inflow tract into the tricuspid orifice.

The records obtained indicate considerable variation in the potential of the cavity of the right ventricle in patients with heart disease and emphasize the importance of drawing no conclusions from a lead made from a single location within this chamber. Records from the pulmonary artery and from the right atrium showed much less variation than those obtained from the right ventricular cavity.

RENAL DYNAMICS IN "ESSENTIAL" HYPERTENSION, THE EFFECT OF SYMPATHECTOMY.—MILTON LANDOWNE, M.D., ALF S. ALVING, M.D., and WRIGHT ADAMS, M.D., CHICAGO, ILL.

Simultaneous studies of blood pressure and Diodrast and inulin clearance were performed upon twelve patients with "essential" hypertension before and up to forty months after sympathectomy. In nine, nonsimultaneous measurements of cardiac output were made. Calculations were made of:

Rk = renal resistance ("afferent plus efferent arteriolar"),
R = resistance of the total measured circulation; and from these
Rn = nonrenal resistance.

If all the data are averaged, there is a slight reduction in renal blood flow after operation, with no essential change in resistances. However, if the cases are divided into three groups according to the changes in blood pressure after c eration, differences between these groups become evident. The data may be preted as follows:

Both renal and total vascular resistances are increased in "essential" tension. Following sympathectomy, the renal resistance may be reduced, ain unchanged, or be increased.

2. The ratio of renal to nonrenal resistance is increased in some cases.
3. The lower the renal resistance, and the less disproportionate the renal to the nonrenal resistance, the greater the likelihood that sympathectomy may

result in a reduction in blood pressure. In such cases sympathectomy may not only effect a reduction in renal resistance, but a proportionately greater reduction in renal than in nonrenal resistance.

The assumptions intrinsic to the formulas used and the small number of subjects studied limit these interpretations to hypothesis.

AURICULAR FIBRILLATION WITH ANOMALOUS A-V CONDUCTION (WPW SYNDROME) IMITATING VENTRICULAR PAROXYSMAL TACHYCARDIA.—Richard Langendorf, M.D., Chicago, Ill.

Observations are reported on a case of mitral stenosis with the Wolff-Parkinson-White syndrome which presented auricular fibrillation and auricular flutter during a final phase of congestive failure. It is shown that the auricular impulses continue to be conducted to the ventricles either over the bundle of His or over the accessory bundle or over both pathways simultaneously giving rise to fusion beats. When conduction takes place exclusively over the accessory bundle, the ventricular rate tends to be very rapid and the record can be easily misinterpreted as ventricular paroxysmal tachycardia; when both types of ventricular complexes are present, those due to conduction via the accessory bundle tend to occur "prematurely" and in groups, imitating ventricular premature systoles. Records are presented showing such pseudobigeminy, trigeminy, and polygeminy. The reports in the literature of paroxysmal tachycardia of ventricular origin in cases of Wolff-Parkinson-White syndrome are reviewed and it is shown that the majority should be correctly interpreted as cases of paroxysmal auricular fibrillation with A-V conduction along the accessory bundle. It is pointed out that the rare occurrence of ventricular paroxysmal tachycardia in patients with this syndrome speaks against the hypothesis of an irritable focus in the ventricles; furthermore, the occurrence of anomalous A-V conduction in the presence of auricular fibrillation rules out the mechanical effect of auricular systole as a factor in the production of the syndrome. Quinidine sulfate was found to act predominantly on the transmission of the impulse via the accessory bundle, whereas digitalis affected predominantly conduction via the A-V node and bundle of His. Either drug used alone failed to slow the ventricular rate appreciably. The combined use of quinidine and digitalis seems to be the medication of choice to slow the ventricular rate in cases of the Wolff-Parkinson-White syndrome and permanent auricular fibrillation.

THE ELECTROCARDIOGRAPHIC PATTERN OF LATERAL WALL INFARCTION.—Richard Langendorf, M.D., Albert J. Simon, M.D, and Louis N. Katz, M.D., Chicago, Ill.

A clinical and electrocardiographic study is presented of thirty cases of recent lateral wall infarction. The diagnosis is based on the characteristic clinical picture associated with recent myocardial infarction and an electrocardiographic pattern characterized by discordant changes in chest Leads CF_2 and CF_5. Typical QRS changes are missing in most instances in the three chest leads (CF_2, CF_4, and CF_5) taken routinely; the S-T segment shows a tendency to be depressed in CF_2 and elevated in CF_5. The limb leads usually show the changes expected with anterior wall infarction; however in the "S-T stage" the changes may be less definite than in the chest leads; in the "T stage" reciprocity in Leads I and III is often missing and T is inverted in all limb leads. Thus, the previously described "T_N pattern" of healing myocardial infarction seems to indicate involvement of the lateral wall of the left ventricle. After recovery the residual electrocardiographic changes tend to take on a nonspecific appearance and no longer permit a diagnosis of remote myocardial infarction. An autopsy was obtained in two cases and confirmed in both instances the diagnosis of recent lateral wall infarction.

EXPERIMENTAL CHAGAS' HEART DISEASE.—F. S. LARANJA, M.D., J. PELLEGRINO, M.D., and E. DIAS, M.D., RIO DE JANEIRO, BRAZIL.

Electrocardiographic, x-ray, and pathologic studies of the heart were carried out on dogs experimentally inoculated with blood from human beings with Chagas' disease or with intestinal contents of bugs infected with *S. cruzi.*

Infected dogs developed a type of heart disease quite similar in several aspects to that found in human beings with Chagas' disease, in its acute and chronic stages.

Similarities between heart disease developed in experimentally infected dogs and that found in human beings with Chagas' disease were particularly striking in the chronic stage of infection. After several months of inoculation, dogs presented enlargement of the heart, particularly of the right cavities, several types of disturbance of cardiac rhythm, and signs of congestive heart failure, with dyspnea, gallop rhythm, edema, and ascites. Death in heart failure or sudden death occurred. The electrocardiographic changes observed in experimentally infected dogs included right bundle branch block, incomplete and complete; ventricular extrasystoles, bigeminal or trigeminal rhythm, or occurring in short runs (extrasystolic ventricular tachycardia); low grades of A-V block; transient A-V dissociation (isorhythmic dissociation); transient primary T-wave changes; atypical QRS changes; and patterns of right ventricular enlargement.

The possibility of reproducing in dogs a type of heart disease quite similar to that found in human beings with Chagas' disease, apart from furnishing convincing evidence as to the validity of the clinical description of chronic Chagas' heart disease as made by Chagas and recently by us, may open a fruitful field for collateral studies on heart disease.

OBSERVATIONS ON THE MECHANISM OF THE WOLFF-PARKINSON-WHITE SYNDROME (WPW) AND OTHER TYPES OF PRE-EXCITATION.—EUGENE LEPESCHKIN, M.D., BURLINGTON, VT.

In thirty patients with the Wolff-Parkinson-White syndrome the potential of the entire chest surface was mapped by means of synchronized unipolar leads. The right or upper posterior hemithorax first develops steady negativity of low voltage. Negativity of high voltage then rotates across the precordium to the left. This indicates that the aberrant initial ventricular excitation originates near the A-V groove.

In one case (observed together with Dr. R. Fremont) P-R first became prolonged during rheumatic fever. A slow initial portion of QRS then appeared, making P-R normal and QRS prolonged. During convalescence P-R became shortened as in the typical Wolff-Parkinson-White syndrome. Here the slow initial portion of QRS was fixed to the rest of QRS, not to P, indicating that aberrant ventricular excitation took place after passage of the A-V node.

In many cases the appearance of the Wolff-Parkinson-White form was preceded or followed by terminal inversion of T in leads which had shown a downward slow initial portion of QRS. A similar relation exists between the direction of QRS and that of the subsequently appearing inverted T in paroxysmal ventricular tachycardia. This indicates local prolongation of activity in regions where the aberrant excitation originates, making increased myocardial excitaity due to myocarditis in these regions a possibility.

RIMENTAL STUDY ON THE MECHANISM OF THE CARDIAC MONOPHASIC ACTION POTENTIAL (MAP).—EUGENE LEPESCHKIN, M.D., BURLINGTON, VT.

1. In frogs and cats the slow "extrinsic" component of the electrocardiogram registered by means of suction electrodes remained unchanged after appli-

cation of suction, but the rapid "intrinsic" component was reversed in direction. The monophasic action potential began when the excitation reached the "normal" electrode, but the difference between the curves between and after injury was reached. The duration of ascent of this monophasic deformation curve decreases with the diameter of the suction electrode and reaches 0.006 second if microelectrodes are used. This apparently corresponds to the ascent of activity in the single muscle fiber.

2. If the muscle surface reverses its polarization during excitation, the muscle interior becoming positive (Curtis and Cole), rapid injury during systole should cause instantaneously a positive injury potential. Actually a positive potential did not develop until the end of systole, when it could be attributed to accelerated repolarization. The fact that the positive monophasic action potential is usually greater than the negative diastolic injury potential must be attributed, in accordance with Katz, to partial depolarization in the vicinity of the injury.

3. If a U wave was present before injury, it was transformed into a negative afterpotential after injury.

CIRCULATORY MODIFICATIONS IN MAN AFTER INGESTION OR INFUSION OF FLUID.—Jean Lequime, M.D., Brussels, Belgium.

1. After the ingestion of 1.0 liter of water, a considerable increase of the cardiac output, and a still larger increase of the systolic output are observed. Thus, the intake of a great amount of fluid results in an increase in cardiac work, and this must be considered in patients with a deficient myocardium. The observed variations are not necessarily related to diuresis, since saline gives a slight diuresis, while water gives a rapid and intense diuresis. They are not the result of an increase of metabolism, for the oxygen consumption does not change noticeably. The increase of the cardiac output should be the result of the increase of the blood volume and of cutaneous, splanchnic, and renal vasodilatation.

2. After intravenous injection of forty c.c. of a 20 per cent sodium chloride solution in normal man, a cardiac acceleration is observed. Venous pressure is increased, the circulation rate is noticeably shorter, and there is a slight increase of the oxygen consumption. The arterial pressure does not undergo any significant changes. The cardiac output increases considerably, apparently because of vasodilatation, especially in the cutaneous tissues. In patients with coronary disease, injection of a saline solution frequently results in changes in the RS-T segment in the electrocardiogram similar to those observed after an exercise test or an anoxemia test. These electrocardiographic changes are probably due to a relative coronary insufficiency attendant upon a greatly increased cardiac output. This method is thus of value in the diagnosis of coronary disease.

ARCHITECTURE OF THE HUMAN VENTRICULAR MYOCARDIUM.—Maurice Lev, M.D., Chicago, Ill., and S. Simkins, M.D., Omaha, Neb.

By a combination of gross and microscopic studies of the human heart, during which the ventricular fibers were unrolled by a modification of Mall's technique, it was found that the concept that four distinct muscles (superficial and deep, sinospiral and bulbospiral) constitute the ventricular wall is in need of correction. The ventricular myocardium consists of one muscular syncytium, made up of fibers arranged in fasciculi of various sizes, both gross and microscopic, some of the former being grouped together to form bands. We have recognized three depths of fasciculi, epicardial, middle, and endocardial, without connotation that any connective tissue cleavage planes separate the syncytium into lamina. By the invagination of fasiculi, the septum is formed, thus demarcating right and left ventricular musculature. The musculature of both ventricles and the septum, however, are all part of one muscular syncytium.

SOME EFFECTS ON THE CIRCULATION OF SMOKING CIGARETTES WITH VARYING NICOTINE CONTENT.—ROBERT L. LEVY, M.D., JAMES A. L. MATHERS, M.D., and MYRON C. PATTERSON, M.D., NEW YORK, N. Y.

Published in full in this issue.

INTRACARDIAC CATHETERIZATION IN THE STUDY OF CONGENITAL HEART DISEASE. I. FINDINGS IN INTERATRIAL SEPTAL DEFECTS.—RUDOLFO LIMÓ LASÓN, M.D., and VÍCTOR RUBIO, M.D., WITH THE TECHNICAL ASSISTANCE OF CRISEIDA GUERRERO, M.D., MEXICO, D.F., MEXICO.

The catheter technique has been applied to the study of fifteen patients with auricular septal defects. Pulmonary, systemic, and shunt flows were calculated. The left auricle was catheterized in ten of our subjects; the pulmonary veins, in eight. The system of using the cavae-auricle oxygen difference will not give the diagnosis in all cases, as evidenced by the fact that the average oxygen difference in our series is 3.11 volumes per cent (range, 1.4 to 4.7).

Although the shunt has been considered to be from left to right, evidence is presented to the effect that in some patients, this may be altered in its entirety or in part. Some patients present, simultaneously, left to right and right to left shunts. This is proved by the fact that the blood taken from the right auricle is arterialized as compared with the average of both cavae, while the sample taken from the left auricle is mixed with venous blood as compared with samples taken from the pulmonary veins. One patient presented a complete reversal of flow; the shunt was directed entirely from right to left. In some patients the left to right shunt seems to increase in the erect position; the right auricle becomes more arterialized on standing.

STUDIES OF FLUOROCARDIOGRAPHY: TRACINGS OF THE LEFT VENTRICLE IN MYOCARDIAL INFARCTION.—ALDO A. LUISADA, M.D., and FELIX G. FLEISCHNER, M.D., BOSTON, MASS.

Twenty patients with old or recent myocardial infarctions were studied by means of fluorocardiography. The graphic study was made in the postero-anterior position and in both anterior oblique positions.

Several abnormalities of ventricular systole and diastole were recognized. Among these, lack of pulsation and inverted pulsation (paradoxical pulsation) in a circumscribed area were considered as the most significant data; the former, pointing to an area of "local paralysis"; the latter, to a "dynamic aneurysm" of the ventricular wall. Evaluations of the dynamic results of such abnormalities are given. The reasons for suggesting the two new terms are discussed. Correlation of the findings with electrocardiographic data revealed a coincidence of about 90 per cent. In general, the area presenting an abnormality of contraction was found to be more extensive than indicated by the electrocardiogram.

The findings confirm those of previous roentgenkymographic studies. The reasons for a greater exactitude and broader applicability of fluorocardiography in comparison with roentgenkymography are given.

CONDUCTION IN RE-ENTRY PATHWAYS IN THE HUMAN HEART.—I. MACK, M.D., CHICAGO, ILL.

The phenomenon of re-entry was investigated by a study of the electrodiogram of patients with ventricular premature systoles which showed so-called fixed coupling with the dominant beats. It was found that while in most patients a fairly fixed time interval was always present between the dominant

beat and the following ectopic ventricular systole, others showed variations in this time interval (labelled R-V interval). Parasystole as a possible underlying mechanism was excluded in the latter cases. The variations in the R-V interval were seen to be dependent on the cycle length immediately preceding it. In some instances the duration of the R-V interval varied with the length of the preceding cycle (prolongation of refractory period as a result of lengthening of preceding cycle), and in others it varied inversely with the length of the preceding cycle (effect of duration of rest period on conduction). In one of the latter cases partial block with 3:2 conduction and the Wenckebach phenomenon in the re-entry pathway was demonstrated. The subsequent development of 2:1 conduction, and eventually complete block (or interference) in the re-entry pathway was also seen.

BLOOD PRESSURE VARIATIONS IN PATIENTS WITH INTERMITTENT CLAUDICATION.—M. R. MALINOW, M.D., B. MOIA, M.D., E. OTERO, M.D., and M. ROSENBAUM, M.D., BUENOS AIRES, ARGENTINA.

A hitherto undescribed mechanism of severe hypertension occurring in patients with intermittent claudication of the lower extremities is reported. A standardized leg exercise, sufficient to produce the characteristic pain, greatly raised the blood pressure of ten patients with intermittent claudication. Differences of 50 mm. Hg in the systolic and/or the diastolic were commonly found. Presumably, the same blood pressure variations occur while the patient is walking, thus greatly increasing the work of an already generally damaged heart. The same exercise did not greatly change the blood pressure in patients unless intermittent claudication developed. These blood pressure variations are reduced by vasodilator drugs (trinitrin, mannitol hexanitrate) and by tetra-ethyl ammonium chloride. The therapeutic implications are obvious. A method is described by which a standardized exercise of the legs is performed before and after a cuff at 280 mm. Hg is placed on the thigh. If the blood pressure variations so induced are compared, the presence or absence of ischemia can easily be detected.

PHENOMENA UNREVEALED BY ELECTROCARDIOGRAPHY WHICH ARE REVEALED BY X-RAY CINE-DENSIGRAPHY.—MAURICE MARCHAL, M.D., PARIS, FRANCE.

Abstract in English not available.

ELECTRO-HEMATOLOGY.—FREDERICO DE MARCO, M.D., ARARAQUARA, E. S. PAULO, BRAZIL.

Abstract in English not available.

OBSERVATIONS ON BLOOD VOLUME AS DETERMINED BY PLASMA DYE DILUTION AND DILUTION OF RED CELLS TAGGED WITH RADIOACTIVE PHOSPHORUS.—H. S. MAYERSON, M.D., ROBERT T. NIESSET, M.D., and CHAMP LYONS, M.D., NEW ORLEANS, LA.

Independent studies in patients on the rate of absorption and of loss of radioactive phosphorus by red cells in vivo and in vitro and of the loss of phosphorous from the plasma in vivo have been made to check the validity of red cell volume determinations by a simple dilution method, using radioactive phosphorous as a tracer. Whole blood samples are used for counting so that no chemical or physical separation of the trace element is required. Discrepancies between whole blood volume calculated from the red cell volumes and that calculated from the plasma volumes as determined by plasma dye (T-1824) are analyzed with refer-

ence to the ratio of plasma volume to red cell volume. Variations in plasma to cell volume ratios are shown to have opposite effects on the apparent volumes so that the results are not directly comparable. Total (body) hematocrits are obtained from the independent measurements of total plasma volume and total red cell volume, and are compared with direct (in vitro) hematocrit readings made from peripheral blood. The variation appears to occur in either direction and to be nonspecific. The body and peripheral hematocrits often show reasonably good agreement in healthy individuals but usually show wide variation in disease. After transfusion there seems to be an unexpected loss in plasma volume and, in some experiments, evidence of trapping of red cells.

SYMPATHETIC COMPONENT OF THE ELECTROCARDIOGRAPHIC RESPONSE TO POSTURE.—H. S. Mayerson, M.D., and Horace L. Wolf, M.D., New Orleans, La.

It was shown in a previous study that the tilting of an individual from the horizontal to the upright (75°) position produces an increase in the amplitude of P_2 and P_3, a decrease in T_1, T_2, and T_3 and T_{IVF}, a shift in the average QRS axis to the right and of the average T axis to the left, and a decrease in the QRS-T area. These results suggested that there are two phases of response to the alteration in posture. When the subject is tilted to the upright position, there is an immediate readjustment of the anatomic axis and a consequent reorientation of the electrical fields surrounding the heart which accounts for some of the changes. Subsequent variations which occurred during the maintenance of the upright position were interpreted as a manifestation of strong sympathetic activity evoked as a compensatory response to the diminished venous return and the tendency to cerebral anemia (and hypoxia).

The present experiments are a continuation of this study, particularly of the role of the sympathetic nerves in the response to tilting. Attempts were made to reinforce the sympathetic component by the administration of epinephrine and of atropine (to minimize or abolish parasympathetic influence). Conversely, ergotamine was administered to diminish or eliminate sympathetic activity and tetra-ethyl ammonium chloride (etamon chloride) was used to block all autonomic ganglia. Our results indicate that the electrocardiographic changes brought on by tilting to the upright position cannot be significantly modified by the use of these parasympatholytic, sympatholytic, or sympathetic reinforcing drugs. The assumption of the upright position evokes a strong sympathetic response which can be modified but not abolished by sympatholytic drugs. The latter diminish the vasomotor compensation but do not significantly alter the pulse rate increase which occurs with the change of position. The administration of a parasympatholytic drug (atropine) intensifies the sympathetic effect, as evidenced by an increased pulse rate over control studies.

THE APPLICATION OF MICROPLETHYSMOGRAPHY TO THE EVALUATION OF PATIENTS WITH HYPERTENSION.—R. S. Megibow, M.D., and A. S. W. Touroff, M.D., New York, N. Y.

Recently, we described an objective method which has proved of value in lecting hypertensive patients who would be benefited by thoracolumbar pathectomy with splanchnicectomy. The procedure entailed an analysis the volume changes in the toes and fingers before and after vasodilatation with nitroglycerine. Pulsatile and nonpulsatile volume fluctuations were recorded by means of a new ink writing photoelectric microplethysmograph.

The present investigation details modifications of the original technique. These consist of determining the rate of peripheral blood flow in addition to measuring the amplitude of both the volume pulse and alpha waves after nitro-

glycerine, and after two other vasodilators, namely, tetra-ethyl ammonium and dihydroergocornine. These drugs induce vasodilatation through different mechanisms, and on the basis of their pharmacologic effects, we have been able to separate patients with "essential" hypertension into two large categories. It has been found that those patients who develop maximal vasodilatation after tetra-ethyl ammonium rather than after nitroglycerine or dihydroergocornine prove to be the ones who will be most benefited by sympathectomy.

Illustrative plethysmograms will be demonstrated and certain concepts concerning the genesis and treatment of hypertension, formulated as a result of these studies, will be discussed.

FURTHER STUDIES ON THE ANTIFIBRILLATORY ACTION OF CORONARY DILATOR DRUGS IN CHLOROFORM-ADRENALINE VENTRICULAR FIBRILLATION.—K. I. MELVILLE, M.D., MONTREAL, CANADA.

In earlier publications from this laboratory, it was shown that the coronary dilator drugs, atabrine and papaverine, can protect the heart against ventricular fibrillation following injection of adrenaline during chloroform inhalation in dogs. It has also been shown that several coronary dilator agents can similarly prevent ventricular fibrillation induced by pituitary extract, a coronary constrictor agent, in phenobarbitalized animals. It was of interest, therefore, to study the influence of various other coronary dilator substances in chloroform-adrenaline ventricular fibrillation. The experiments to be described concern the influence of ephedrine, sodium nitrite, amyl nitrite, nitroglycerine, and diethylaminoethoxy-2-diphenyl (F-1262 or Dacorene) on this type of fibrillation.

Dogs anesthetized with sodium pentobarbital were used. Artificial respiration was maintained throughout by means of a Starling pump. In order to induce ventricular fibrillation, chloroform was administered for five minutes, following which adrenaline (0.02 mg. per kilogram) was injected. Smaller doses of adrenaline (0.002 mg. per kilogram) under similar conditions usually induced only ventricular extrasystoles but no fibrillation. The agent to be tested was injected during the chloroform inhalation, generally two to three minutes before the adrenaline. Blood pressure changes and electrocardiograms (Lead II) were recorded. In some animals the vagi were cut. All injections were made intravenously.

Under the described conditions, it was observed that ephedrine sulfate (2.5 to 5.0 mg. per kilogram), sodium nitrite (10 to 20 mg. per kilogram), amyl nitrite (15 to 20 secs. inhalation), nitroglycerine (0.1 to 0.5 mg. per kilogram), and diethylaminoethoxy-2-diphenyl hydrochloride protected the heart both from the cardiac irregularities observed after small doses of adrenaline and from fatal ventricular fibrillation after large doses of adrenaline. In a few experiments also, after induction of chloroform-adrenaline ventricular fibrillation, intracardiac injection of the latter compound in conjunction with cardiac massage stopped the fibrillation and a normal coordinated heart beat was restored. The blood pressure and electrocardiographic changes associated with these phenomena will be discussed.

The results appear to support the view that in chloroform-adrenaline ventricular fibrillation, impairment in myocardial nutrition is an important factor, and that the antifibrillatory actions of the agents used are due mainly to their coronary dilator actions. Whether this favorable effect of these drugs is due directly to offsetting some existing coronary constriction or indirectly to the improved blood supply to the myocardium cannot be stated.

CIRCULATORY EFFECTS OF A NEW SULPHURIC ESTER OF GLYCERIN.—Rafael Méndez, M.D., José Pisanty, M.D., and Ernesto Sodi P., M.D., Mexico, D.F., Mexico.

Trisulphoglycerin, synthesized from glycerin and Nordhausen's acid, causes the following effects:

1. In the anesthetized (Dial), eviscerated, and adrenalectomized cat, in maximal doses of 15 mg. per kilogram, there is a marked rise in arterial pressure (which lasts ten to thirty minutes), bradycardia, and often decreased pulmonary ventilation; probably due to bronchial spasm.

2. In the adrenalectomized dog, doses of 5.0 mg. per kilogram cause a clear hypertensive effect only after complete denervation of the carotid sinus and section of the vagi and depressor nerves. Higher doses produce cardiac irregularities which mask the pressor effect.

3. In the heart-lung preparation with heart failure induced by Nembutal, trisulphoglycerin in doses of 20 mg. produces a slight and transitory improvement, which appears as a decrease of venous pressure and a slight increase of output.

4. In the isolated rabbit ear a direct vasoconstrictor effect can be demonstrated.

Sulphuric esterification of glycerin and other radicals (new synthetic compounds under study) seems to confer hypertensive properties on the resulting compound.

NORMAL CIRCULATORY AND BLOOD VALUES IN ACCLIMATED PERSONS LIVING AT A HIGH ALTITUDE.—Jorge Meneses Hoyos, M.D., Mexico, D.F., Mexico.

Abstract in English not available.

THE ELECTROCARDIOGRAM IN EXPERIMENTAL ANOXIA.—Jorge Meneses Hoyos, M.D., Mexico, D.F., Mexico.

Abstract in English not available.

OBSERVATIONS ON THE SURVIVAL OF PATIENTS AFTER RECENT MYOCARDIAL INFARCTION—G. Y. Mills, M.D., F. Cisneros, M.D., Mexico, D.F., Mexico, and L. N. Katz, M.D., Chicago, Ill.

Five hundred seven patients with recent myocardial infarction were studied to determine the factors concerned in the long term prognosis. In five to six years 81 per cent of the patients were dead. About one-fourth of the patients died in the first two months, about one-half were dead at the end of a year, about two-thirds at the end of the third, and approximately four-fifths at the end of five years.

Hypertension on admission had no effect on the mortality rate in the first two months but caused a slight increase in the long term mortality. Similarly, the presence of known angina pectoris at the time of admission had no deleterious effect on the immediate mortality in the first two months, but the average duration of life of those dying after two months was somewhat shortened. In contrast, the presence of heart failure on admission sharply increased the immediate and over-all mortality rate and shortened the average duration of life of those dying after two months. The presence of diabetes mellitus on admission increased the immediate and over-all mortality rate but did not greatly alter the long term mortality. The absence of low voltage, heart block, ectopic rhythms, and sinus tachycardia caused a much better immediate prognosis, but the long term

prognosis was no better than for the whole group. Patients who were asymptomatic on admission had an immediate mortality rate little different from that for the entire group, but the long term mortality rate was better. The immediate mortality rate was greater for women, but after two months the mortality rate was less for women than men. The immediate mortality rate was little affected by location of infarct but after two months was better for lateral wall infarcts than for anterior and posterior infarcts.

THE ELECTROCARDIOGRAM IN "IN EXTREMIS." CLINICAL DEATH AND BIOLOGICAL DEATH.—Augusto Mispireta Dibarbout, M.D., Carlos Guibovich, M.D., and Jorge Neira, M.D., Lima, Peru.

Electrocardiograms were taken in human subjects (children and adults) and dogs in "in extremis," clinical death, and cellular or biological death. The death of the animals was produced by bleeding; human subjects died because of various diseases (two with skull fractures). Continuous electrocardiographic tracings were obtained, in some cases from the beginning of "in extremis."

We have differentiated, as other authors have done, the three periods: "in extremis," clinical death, and biological death. The last period was studied exclusively in relation to the cardiac electric activity. The time between clinical and biological death was variable with an average between three to seven minutes. The longest duration was fifty-four minutes, in a case of skull fracture. During "in extremis" there was always sinus tachycardia. Simultaneous with clinical death were the most varied modifications of rhythm, rate, and conduction. The final cardiac standstill occurred in one-half of the cases through auricular standstill and in the other one-half through ventricular standstill. Intracardiac injections of adrenalin did not significantly alter the electrocardiograms.

EFFECT OF THE INHALATION OF OXYGEN ON THE ELECTROCARDIOGRAPHIC CHANGES INDUCED BY EFFORT IN ANGINA PECTORIS.—B. Moia, M.D., and F. F. Batlle, M.D., Buenos Aires, Argentina.

Twelve patients with angina pectoris on effort and normal electrocardiograms at rest, but showing signs characteristic of myocardial ischemia on effort, were chosen for the study. Once the electrocardiogram became normal and after two hours rest following the effort, the same test was performed but having the patients inhale pure oxygen before, during, and after its execution. The electrocardiograms of the second test again showed changes similar to those previously registered. It is concluded, then, that the inhalation of 100 per cent oxygen is not capable of preventing the myocardial ischemia provoked by effort in anginal patients.

These findings confirm the general clinical impression which the authors have obtained from the use of oxygen administered correctly in concentrations varying from 50 to 100 per cent, during many years of practice, in patients with coronary diseases. They conclude that its therapeutic efficiency is slight or doubtful, except when there are disturbances of hemorespiratory function, a profound state of shock, or any other complication which would justify its use. This refers particularly to the use of the costly oxygen tent.

COMPARATIVE STUDIES ON THE ORAL AND INTRAVENOUS ADMINISTRATION OF DIGITALIS PURPUREA LEAF PREPARATIONS IN MAN.—B. Moia, M.D., and M. Monguel, M.D., Buenos Aires, Argentina.

The effects of oral and intravenous administration of digitalis leaf preparations were studied in numerous patients with permanent auricular fibrillation

and in normal subjects, by observing the modifications in cardiac rate and in the electrocardiogram.

Three types of comparative observations were carried out: (1) Digitalization with daily intravenous doses of 0.40 Gm. (exceptionally 0.60 Gm.) until a manifest therapeutic effect was obtained, attempting not to provoke vomiting, followed by a daily maintenance dose of 0.20 to 0.10 Gm. during ten days or more and then the same dose by mouth for fifteen or more days. (2) Similar doses to those in (2), but starting with the oral route and following with the intravenous. (3) In patients under chronic oral digitalization, administration of the same dose by the intravenous route for fifteen or more days.

The results obtained show that with these doses, the therapeutic and electrocardiographic effects, like those on heart rate in auricular fibrillation, are practically the same, whichever route is used.

THE USE OF FLUORESCEIN FOR THE ESTIMATION OF THE ADEQUACY OF BLOOD FLOW IN THE EXTREMITIES.—M. H. Nathanson, M.D., R. Merliss, M.D., and S. R. Elek, M.D., Los Angeles, Calif.

In a previous study it was shown that the circulation time to an extremity could be studied by the application of a histamine wheal on the extremity and the determination of the time of appearance of fluorescence in the wheal after the injection of fluorescein in an arm vein. There was a prolongation of this fluorescein-wheal circulation time in individuals with peripheral vascular disease. In the present report, the method has been extended to a larger number of patients and certain modifications have been followed and compared with the original procedure. In cases of peripheral gangrene in which amputation was considered, the fluorescein test was used to ascertain the line of demarcation between the skin receiving an adequate circulation and that to which the blood supply was definitely reduced. The use of multiple wheals demonstrated the point at which a definite prolongation of circulation time occurred. Another procedure was to make a linear scratch in the skin from above the knee to the ankle. Following the injection of fluorescein, a bright fluorescence is observed in the upper portion of the scratch, the fluorescence disappearing abruptly at a definite point. In the control extremity, good fluorescence can be seen throughout the entire length of the scratch. The results of amputation and the examination of the amputated extremities suggest that this provides a good method for the estimation of the adequacy of the circulation to the skin. An interpretation of circulation time measurements in terms of minute volume flow in the extremities is discussed.

STUDIES RELATIVE TO THE CHEMOTHERAPY OF BACTERIAL ENDOCARDITIS.—M. H. Nathanson, M.D., and R. A. Liebhold, M.D., Los Angeles, Calif.

The introduction of a successful therapeutic agent often leads to a clarification of the nature of a disease. The uniformly fatal character of bacterial endocarditis prior to the advent of penicillin and the failure of various therapeutic agents has not been adequately explained. It has been suggested that failure of antibacterial agents is due to an inhibiting or retarding effect by the fibrin on the diseased valves. In a previous study it was shown that sulfonamide compounds showed antibacterial activity on seeded agar plates but failed to do so on seeded fibrin plates. Penicillin was equally active on both media.

In the present study it was shown that fibrin or fibrinogen had no inhibiting action on sulfonamides, indicating that their inactivity was due to a failure to penetrate fibrin adequately. Also at autopsy fragments were taken from the

surface and deep portions of vegetations and placed on seeded agar plates. The zones of inhibitions surrounding the fragments were equal for the deep as compared with the surface portions, indicating a free diffusion of penicillin into the vegetation. In vitro studies demonstrated that streptomycin also diffuses freely into fibrin.

These studies indicate that the therapeutic efficiency of a compound in bacterial endocarditis depends on its ability to penetrate fibrin. The experiments also tend to minimize the importance of anticoagulants in this disease since fibrin has no retarding effect on the activity of penicillin and streptomycin.

THE CARDIOVASCULAR EFFECTS OF THE INTRANASAL ADMINISTRATION OF MECHOLYL.—M. H. NATHANSON, M.D., AND J. TOBER, M.D., LOS ANGELES, CALIF.

Supraventricular tachycardias are most effectively treated by stimulation of the vagus innervation to the heart. This may be accomplished (1) mechanically by pressure on the carotid sinus and (2) chemically by the administration of Mecholyl subcutaneously. These procedures require therapy by a physician or nurse. The effect of the sublingual administration of Mecholyl was studied. A local effect, salivation, was noted but no systemic effects were observed. However, on intranasal application of Mecholyl prompt systemic effects were observed. Such an action has previously been reported by Wright and his associates. The purpose of the present study was to determine whether the effects of a therapeutic dose of Mecholyl given subcutaneously could be produced by intranasal administration.

In a group of hypertensive patients Mecholyl was administered intranasally and subcutaneously. The depressor effect of 25 mg. subcutaneously could be completely and promptly produced by the administration of 200 to 300 mg. intranasally. The intensity of other systemic effects, flushing of face, sweating, salivation, and lacrimation, was the same after both methods of administration. On intranasal application, the action was as prompt as that observed after subcutaneous injection. Cardiac effects demonstrated by the electrocardiogram, such as varying degrees of heart block and cessation of auricular tachycardia, were observed after the intranasal administration of the drug. The conclusion is that a therapeutically effective dose of Mecholyl can be administered by the intranasal route.

THE PARADOXICAL EPINEPHRINE-ACETYLCHOLINE REACTION IN CORONARY INSUFFICIENCY.—ROBERT L. NELSON, M.D., DULUTH, MINN.

Attention is directed to a physiologic mechanism which is an important factor in the production of some cases of acute coronary insufficiency. Certain persons display paradoxical responses to adrenalin and to acetylcholine. The usual response to adrenalin is an increased pulse rate, increased blood pressure, palpitation, and, in some cases, visible constriction of the retinal arteries or blanching of the skin. Acetyl-beta-methylcholine chloride usually produces the opposite effect.

In cholinergic individuals of high autonomic tone this is probably a more frequent mechanism in the production of coronary artery spasm than the literature indicates. It is probably one of the most easily prevented forms of coronary catastrophies and definitely one that should be recognized in all cases of autonomic study. A simple means of advance recognition and some clinical illustrations are presented.

THE BALLISTOCARDIOGRAPHIC PATTERN, WITH SPECIAL REFERENCE TO THE H-WAVE.—John L. Nickerson, M.D., New York, N. Y.

The origin of the various portions of the ballistocardiographic pattern is demonstrated by the use both of models and of clinical material. One serious objection to the model method of testing different circulatory situations has been that fluid ejection in the model produces immediate movements of the ballistic system, whereas with human ventricular ejection the movement of the ballistic system appears to be delayed by .02 to .03 second. In the work presented here we have been fortunate in obtaining records where the auricular and ventricular patterns were sufficiently separated so that the effect of the auricular complex in causing this apparent delay was revealed.

A CLASSIFICATION OF CONGENITAL CARDIAC DISEASES BASED UPON HEMODYNAMIC PRINCIPLES: ITS USEFULNESS FOR CLINICAL DIAGNOSIS.—Sergio Novelo, M.D., and Rodolfo Limón, M.D., Mexico, D.F., Mexico

It is considered that the alteration of circulatory dynamics in congenital cardiac cases is fundamentally responsible for the clinical and pathological findings. Regardless of the wide variety of anatomical types, the end result of the morphological defects is the creation of several circulatory patterns. Clinically speaking, it is not always possible to recognize the exact anatomical nature of circulatory alteration in most of the cases. Furthermore, surgery is able to correct or alleviate the altered circulation, either by surpressing anatomical defects or by creating compensatory mechanisms. Thus, in the present state of knowledge, what the clinician should accomplish is to individualize the patient's circulatory pattern and to ascertain if it is amenable to surgical correction. These facts stress the necessity of grouping congenital malformations of the heart within hemodynamic patterns. We believe that a classification of this sort will be useful in clinical work.

The authors present their own classification.

FURTHER STUDIES OF THE CIRCULATION WITH RADIOACTIVE ERYTHROCYTES.—Gustav Nylin, M.D., and S. Hedlund, M.D., Stockholm, Sweden.

Published in full in this issue.

MECHANISM IN WENCKEBACH'S PERIODS AND ELECTRICAL ALTERNANS.—Richard F. Öhnell, M.D., Stockholm, Sweden.

Earlier studies regarding the mechanism in these conditions have emphasized the significance of insufficiency recovery from one beat to the other.

Öhnell and Anderson, 1946, and Öhnell, 1946, have reported cases where autonomic inhibitory effects seemed to dominate the picture in certain cases of Wenckebach periods. Periodicity was related to respiratory movements. The intimate connection with respiration has been further elucidated. Increased respiratory frequency gives fewer conducted beats per period. For a short while before the spontaneous disappearance of the periodicity, one period may occur at every other breath. "Aberrant" configuration of single periods may be explained by altered length of the respiratory cycles, and so forth.

As an explanation of this phenomenon, it is assumed that varying autonomic activity inhibits the A-V conduction. Furthermore, some mechanism or other will cause a return to a normal P-R interval after every dropped ventricular

beat. Electrical alternans may in some cases be due to the presence of an additional excitatory spread in the ventricles during every second beat ("concealed pre-excitation").

MECHANISM IN PRE-EXCITATION. THE "CACIVA" TECHNIQUE. ASSAY OF QUINIDINE EFFECT.—Richard F. Öhnell, M.D., Stockholm, Sweden.

"Pre-excitation" indicates the presence of an abnormal (additional) excitatory spread in the ventricles, chronologically bound to auricular activity. It causes a slightly premature excitation of the area to which it spreads (Acta Med. Scandinav. suppl. 152, 1944).

By comparing the times required for depolarization of the ventricles during different functional states in the same case of pre-excitation, the role, if any, of the normally conducted wave from the auricles has been further elucidated. In sixteen or more of about eighty-five cases, the normally conducted wave seemed to play no role or only an inconspicuous one. In the majority of the pre-excitation cases, however, the abnormal as well as the normal wave participates in ventricular excitation during the pre-excitation beat. In but one of the sixteen cases was there a "kink" in the ascending limb of QRS. Comparatively late arrival rather than nonarrival of the normally conducted wave seems to explain its restricted role in these sixteen cases.

A report is given on the so-called Caciva technique, developed by the author. Different instruments (ten are presently available) are introduced into the thorax via a vein and an artery in the neck. Theoretical, diagnostic, and therapeutic problems are attacked in both dogs and man.

Öhnell and Obreschkov, 1948, used pre-excitation cases for biological assay of quinidine. However, there may be great variations in "quinidine need" from time to time in one and the same case. Öhnell, 1948, studied the part played by the auricles in pre-excitation. Kjellbeg and Öhnell, 1948, registered the movements of the x-ray heart shadow in pre-excitation cases as well as in cases with extrasystoles and impaired intraventricular conduction.

A STUDY OF ALLEGED INTER-CORONARY REFLEXES FOLLOWING CORONARY OCCLUSION.—David F. Opdyke, M.D., and E. E. Selkurt, M.D., Cleveland, Ohio.

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BLOOD PRESSURES OF CHRONIC HYPERTENSIVE DOGS SURVIVING BILATERAL NEPHRECTOMY.—B. S. Oppenheimer, M.D., Stephen S. Rosenak, M.D., and Gordon D. Oppenheimer, M.D., New York, N. Y.

The failure of bilateral nephrectomy to abolish the experimental chronic hypertension of rabbits (Pickering) and of three dogs (Grollman) has previously been reported. The period of survival after bilateral nephrectomy was short; at most, four days in Pickering's experiments and three days in Grollman's.

By the use of peritoneal lavage (technique of Rosenak and Siwon, 1926) in three hypertensive dogs (Goldblatt method), the period of survival was prolonged by us to five, six, and nine days, respectively. In our three dogs which had been hypertensive for 1,055, 330, and 336 days previous to removal of the second kidney, the hypertension was maintained almost until death.

Peritoneal dialysis with a modification of Tyrode's solution was carried out on three dogs twice, twice, and three times, respectively, each time using about 20 liters over a period of seven hours. Substantial amounts of nitrogenous crystalloids were eliminated from the blood stream, in addition to which colloidal constituents like proteins were washed out in considerable amounts. Thus,

in addition to the removal of crystalloid toxins and nitrogenous waste products, unknown high molecular substances were also removed from the blood stream. While the blood proteins were replenished from the body stores, after removal of both kidneys no such replacement of a humoral hypertensive factor originating from the kidney was possible. If a humoral hypertensive factor was still operative in maintaining hypertension, it should quickly disappear after bilateral nephrectomy because of the rapid destruction of the hypertensive substance.

INCIDENCE OF THE CARDIOPATHIES IN 1,138 CHILDREN OF THE PUBLIC SCHOOLS IN URUGUAYANA.—Francisco Orcy, M.D., Uruguayana, Brazil.

1. Study of 1,138 children of the public schools in Uruguayana from April to August of 1947 revealed 146 suspected cardiacs, fourteen acquired organic cardiopathies, one congenital cardiopathy, and thirty-eight potential cardiacs, or, respectively, 12.82 per cent, 1.30 per cent, 0.008 per cent, and 3.33 per cent.

2. In the organic cardiopathies, rheumatic fever was the principal etiological factor; it appeared in ten of the fourteen cases (71.43 per cent).

3. In potential cardiacs, rheumatic fever was suspected in 50 per cent.

4. The congenital cardiopathy was a patent ductus arterious.

5. The sedimentation rate was increased in twelve acquired organic cardiopathies (85.71 per cent) and was normal in two. The Wassermann reaction was positive in one case, negative in twelve, and doubtful in four.

6. The sedimentation rate in potential cardiacs was increased in thirty-one cases (81.57 per cent) and was normal in seven. The Wassermann reaction was positive in one case, negative in thirty-three, and doubtful in four.

7. The incidence of organic cardiopathies was larger in subjects 9 to 12 years of age, with an average, respectively, of 17.12 and 15.75 per cent. Of the 1,138 children examined, male subjects (57.53 per cent) dominated over female subjects (42.45 per cent).

8. Among the cardiopathies there were seven cases of mitral cardiovalvulitis; aortitis was next frequent; and least frequent was cardiomyovalvulitis, three cases.

9. There were 101 phonoelectrocardiograms, of which eighty-six showed normal axis shift; eleven, deviation to the right; and four, to the left.

10. A history of epistaxis was found frequently in the patients with cardiopathies as well as in those with epidemic parotitis.

APEX BEAT IN RHEUMATIC AND LUETIC AORTIC INSUFFICIENCIES. ITS RELATION TO NECROPSY FINDINGS.—Teófilo Ortiz y Ramírez, M.D., and Francisco Galland Naredo, M.D., México, D.F., Mexico.

A comparative study has been made between the precordial data gathered from the palpation of the apex and the necropsy diagnosis in cases of aortic insufficiency of either rheumatic or syphilitic origin. In cases in which necropsy findings proved that the myocardial disturbances, most probably myocarditis existed, it was noticed that the apex beat possesses the classical characteristics of Bard's "dome apical impulse" only in pure rheumatic aortic insufficiency. This sign was investigated by radiologic and electrocardiographic study as well as by the clinical data in each case.

THE PARTICULAR IMPORTANCE OF SPECIAL ELECTROCARDIOGRAPHIC LEADS.—Harold E. B. Pardee, M.D., New York, N. Y.

Precordial leads from the usual six precordial points are discussed, with emphasis on the general information about the heart's electrical activity to be obtained from precordial leads and the particular information to be gained from variations of the curve in different precordial areas. Special precordial points are recommended to record auricular activity. Esophageal leads are considered analogous to precordial leads; they merely lead off from a different aspect of the heart's surface.

The effect upon the precordial electrocardiogram of placing the remote electrode upon different limbs is studied in comparison with the use of the central terminal. A method is presented to determine from the deflections in the standard leads which extremity, when paired with any precordial point, will give the most negative (or least positive) deflection. Indications are deduced for the special value of CF leads, CR leads, CL leads, and V leads for different purposes.

Unipolar limb leads indicate the character and degree of modification of the precordial electrocardiogram to be expected when precordial points are paired with an electrode on the extremity. The information afforded by these leads regarding the electrocardiographic position of the heart is discussed and its relation to analogous information obtained from precordial leads. The contribution of unipolar limb leads to the diagnosis of myocardial disease is pointed out.

ON THE SIGNIFICANCE OF THE MIDDLE ARCH.—Ramiro H. Pavón-Caballero, M.D., Holguin, Cuba.

After reviewing the pathology of the left middle arch of the cardiac silhouette ("middle arch"), and after examining x-ray plates of our cases and those in the literature, we have reached the following conclusions:

1. The pathology of the "middle arch" is important and has its own characteristic picture.
2. It is the keystone in the diagnosis of congenital heart disease, both in children and adults.
3. It also has an important characteristic in mitral, congenital, or acquired disease.
4. X-ray plates showing any pathology of the middle arch must be followed in every case by oblique views and by frontal projections (both P-A and A-P), in order to establish its auricular, pulmonic, or aortic nature.
5. The angiocardiogram, especially the "levo-angiocardiogram" permits the determination of the extrinsic or intrinsic condition involved. Castellanos, Pereiras, and associates also detect hypertrophy of left lobe of the thymus by means of their procedure: the "pneumo-mediastino-anterior."
6. We adopt the classification of Castellanos and associates, as it is close to the true cardiological meaning.
7. We consider as cardiovascular those abnormal middle arches produced by myxedema and by thyrotoxicosis.

PERICARDITIS WITH ACTIVE PRIMARY GHON TUBERCULOSIS.—Albert A. F. Peel, M.D., Glasgow, Scotland.

Two simultaneously observed cases are reported:

A previously healthy boy of 11 years developed a harsh cough, and examination revealed pericardial friction and effusion. X-ray films showed a primary active Ghon lesion in left upper lobe, hilar gland enlargement, and pericardial effusion. An electrocardiogram showed pericardial T-wave inversion and

"M complexes" in CR_2. Cough was his only symptom throughout; even when he was febrile, tachycardia was slight and he was bright and cheerful. The effusion absorbed in four weeks and so far (four months) there is no pericardial thickening.

A boy of 14, admitted with an active Ghon focus, hilar gland enlargement, and secondary infiltration of base of right upper lobe, had atypical rheumatism when 11 years of age and again two months before our observation. There was a mid-diastolic mitral murmur, slight convexity of pulmonary artery, and slight enlargement of left auricle. Pericardial friction developed after admission, lasted four days, and was not followed by effusion. The Mantoux test was positive. Leucocytes, 12,500; lymphocytes, 5,500 (44 per cent). He was afebrile with insignificant tachycardia. Four months later the heart shadow was normal but the secondary pulmonary lesion was extending.

The mildness of the constitutional symptoms, and the persistence of friction in the presence of effusion is stressed, reference being made to additional cases of acute tuberculous pericarditis. The etiology of Case 2 is discussed.

DISSECTING ANEURYSM OF THE INTERVENTRICULAR SEPTUM CAUSING OBSTRUCTION OF OUTFLOW TRACT OF RIGHT VENTRICLE, SECONDARY TO CORONARY OCCLUSION.—Albert A. F. Peel, M.D., Glasgow, Scotland.

A woman, 59, who had had no previous cardiac symptoms, developed nausea, vomiting, and pain between the scapulae on April 5, 1946. Vomiting recurred four days later; no abnormality was noted in heart or lungs. She stayed in bed one week. On April 26, 1946, she suddenly became breathless and a loud cardiac murmur was noted. When she was referred ten days later, breathlessness was severe; she had a gray complexion, pale, cyanosed lips, congestion of the bases of the lungs, enlarged liver, and lumbar edema. The heart was enlarged with a widespread murmur suggesting the bruit de Roger, but no thrill. The pulse was barely perceptible, the blood pressure not measurable. She died the next day.

Autopsy showed old infarction at the apex of the left ventricle with more recent infarction of the interventricular septum. A round aperture at the upper anterior portion of the septum led into a disseting aneurysm; this tracked forward toward the right, then downward toward the apex, but without actually perforating into the right ventricle, from which it was separated by a thin layer of endo- and myocardium. It produced a sausage-shaped swelling projecting into the outflow tract of the right ventricle and caused mechanical obstruction.

CLINICAL SIGNIFICANCE OF THE DELAYED INSCRIPTION OF THE INTRINSIC DEFLECTION IN RIGHT PRECORDIAL LEADS.—Ruben Pellón, M.D., and Demetrio Sodi-Pallares, M.D., Mexico, D.F., Mexico.

The clinical significance of the delayed inscription of the intrinsic deflection (DID) is studied in the right precordial leads of 179 cases reaching autopsy. Intrinsic deflection above 0.04 second in V_1 was considered abnormal. The cases were classified into four groups:

Group I.—Valvular heart disease, 125 cases. In forty-seven cases with left valvular defects, the intrinsic deflection was found to be delayed in 12.7 per cent. In seventy-eight cases with added tricuspid lesions, the intrinsic deflection was delayed in 65 per cent. In heart diseases with valvular lesion, an intrinsic deflection delay in V_1 strongly suggests an added tricuspid lesion (fifty

out of fifty-six cases, or 89.2 per cent). Right bundle branch block was coincident with an added tricuspid lesion in six out of seven cases (85.7 per cent). Incomplete right bundle branch block had the same value in twelve out of thirteen cases (92 per cent).

Group II.—Cor pulmonale, fifteen cases. Delayed intrinsic deflection was found in 67 per cent. In five, intrinsic deflection was normal and two of these had left bundle branch block.

Group III.—Congenital heart disease, five cases. Three had a delayed intrinsic deflection, one each an Eisenmenger complex, cor biloculare, and transposition of the great vessels. Two had normal intrinsic deflection; the conditions were coarctation, patent foramen ovale.

Group IV.—Miscellaneous, thirty-four cases (glomerulonephritis, myocardial infarction, and so forth). There was no delayed initial deflection in 91.2 per cent and delayed initial deflection in 8.2 per cent (one of these had right bundle branch block). No correlation was found between delay in the initial deflection and the thickness of the right ventricular wall, nor with the degree of dilatation of the chamber.

PENICILLIN IN CARDIOVASCULAR SYPHILIS.—Aurelio Peralta V., M.D., and Luis Castaneda P., M.D., Lima, Peru.

Twenty-five patients were treated. Two had aortic insufficiencies (one in acute cardiac insufficiency), two had aneurysms, one had myocarditis, one had coronary stenosis (infarct) and aortitis, and some had coronaritis. Serial electrocardiograms and serological reactions were taken fifteen days after treatment and every two months. Penicillin "G" was used in increasing doses, 2,500 units being the initial dose, when there were evidences of coronary alterations. Higher doses, 50,000 to 100,000 units, were used. Total dose was 4,500,000 to 8,000,000 units.

Penicillin produced adverse clinical symptoms in 28 per cent; only in 3.9 per cent did they lead to pain. It was not necessary to stop treatment. In 7.8 per cent of those who presented clinical symptoms, electrocardiographic alterations appeared. However, these appeared without clinical symptoms. Moreover, they were temporary, disappearing eight to fifteen days later. One patient with cardiac insufficiency died one month after the end of the treatment.

The number of instances of increased and decreased serologic reactions were in equal proportion. The increase of the reactions had no relationship to the appearance of clinical or electrocardiographic abnormalities. When the serologic reactions diminished, they came back to their initial intensity four months later. Teleradiography did not change even after two years of treatment. Penicillin, although not harmless, can be used without danger to the patient's life.

REMARKS ABOUT 500 CASES OF CARDIOVASCULAR CONGENITAL MALFORMATIONS EXAMINED IN THE CARDIOLOGICAL DEPARTMENT OF THE INFANTS' MUNICIPAL HOSPITAL IN HAVANA DURING THE LAST THIRTEEN YEARS.—Rodolfo Perez de los Reyes, M.D., Horacio de la Torre, M.D., and Roberto Douglas; Havana, Cuba.

The authors present seventeen lantern slides in which they summarize the clinicostatistical data concerning 500 cases of congenital cardiovascular malformations.

THE SERIAL TOMOGRAPHIC STUDY OF THE THORAX IN THE DIAGNOSIS OF THE ANEURYSMS OF THE CONUS, TRUNK AND BRANCHES OF THE PULMONARY ARTERY.—ARMANDO PEREZ SIMON, M.D., AND FIDEL AGUIRRE, M.D., HAVANA, CUBA.

The usefulness of the tomography for the diagnosis of the dilatations of the conus, trunk, and branches of the pulmonary artery is demonstrated. Radiography and fluoroscopy give only superimposed pictures which cannot be studied apart. This is accomplished by tomography by means of a special technique which *localizes* the organ under study. When a bulging at the left border of the cardiovascular silhouette is noticed, it can be identified only with the tomographic cuts, which are made from the sternum to the vertebral column. Clinical cases of aneurysm of the conus and branches of the pulmonary artery are presented, with radiograms, kymograms, electrocardiograms, and serial tomograms, by means of which the diagnosis is made.

It is concluded that tomography offers a great contribution to the diagnosis of aneurysms and dilatations of the entire pulmonary artery tract. Its application is not difficult. In cases of aneurysm of the left branch of the pulmonary artery, only tomography makes it possible to observe whether there is a dilatation of the trunk. It is also very useful in cases of dilataion of the right branch. In one of our cases, the dilatation from the conus up to the divisions of the left branch was clearly visible, similar to an angiocardiogram.

PERIPHERAL ATERIAL EMBOLISM.—SAMUEL PERLOW, M.D., CHICAGO, ILL.

Forty cases of peripheral arterial embolism are reported; seven at the bifurcation of the aorta, twelve in the iliac, six in the femoral, six in the popliteal, one in the posttibial, five in the axillary, three in the branchial, and one in the ulnar artery. Of these, thirty-one (77.5 per cent) were due to auricular fibrillation, eight (20 per cent) to coronary thrombosis, and one (2.5 per cent) to subacute bacterial endocarditis.

Conservative treatment alone resulted in a viable extremity in twenty-five cases (62.5 per cent). Embolectomy after failure of conservative therapy resulted in improvement in two of seven cases, making a total of twenty-seven cases (67.5 per cent) improved.

Treatment consisted of: (1) Sympathetic block with procaine every two to four hours; (2) papaverine ½ to 1 grain intravenously every two hours; (3) anticoagulants, heparin, 50 to 100 mg. intravenously every four hours and Dicumarol, 300 mg. orally immediately; (4) whiskey as tolerated; (5) elevation of the head of bed to keep extremity dependent; (6) keeping room warm and wrapping the extremity in wool without external heat; (7) embolectomy after 4 to 8 ours' trial of conservative treatment.

AMPUTATION FOR PERIPHERAL VASCULAR DISEASE.—SAMUEL PERLOW, M.D., AND HAROLD A. ROTH, M.D., CHICAGO, ILL.

Analysis of 165 amputations for peripheral vascular disease performed at the Michael Reese Hospital during a twelve-year period (1936 through 1947) revealed an over-all mortality of 17.5 per cent. With the advent of penicillin and more frequent blood transfusions, the results improved and the mortality dropped from 25.0 per cent in 1936 to 1938 to 11.7 per cent in the period between 1945 and 1947. The element of sepsis has been eliminated for the most part and the recent deaths following amputation have been due mainly to cardiovascular accidents.

Local refrigeration of the gangrenous limb plus a proximal tourniquet has enabled us to tide the septic patients over the acute period and to carry out such preoperative measures as correction of the fluid and electrolyte balance, the ketosis and hyperglycemia, the hypoproteinemia, and the anemia, and to administer large doses of penicillin. By these means the amputation was changed from an emergency in a poor-risk patient to one of election in a properly prepared patient.

Preliminary lumbar sympathetic ganglionectomy permitted us to save the knee in a number of patients who would otherwise have required supracondylar amputation.

PATHOLOGY OF THE CARDIAC ATRIA. AN ANATOMIC-ELECTROCARDIOGRAPHIC CORRELATION BASED ON A STUDY OF EIGHTY-FIVE HUMAN HEARTS.—C. L. Pirani, M.D., and R. Langendorf, M.D., Chicago, Ill.

Eighty-five human hearts were studied at autopsy with particular regard to the pathologic changes in the atria. In fifty-five of these, electrocardiograms were available and a correlation study was made between the anatomical changes and the abnormalities of the auricular deflection. The series included several normal hearts serving as controls. Particular attention was paid to the predominance of anatomical changes in the right or left atrium. No attempt was made to study the specific system. In addition to hypertrophy and dilatation, the main pathologic findings in the atria were different degrees of interstitial fibrosis and coronary arteriosclerosis. Irrespective of the cause, there was a general tendency for the changes to be more marked in the right than in the left atrium. Electrocardiographically, the cases were divided in the following groups, depending on the auricular rhythm and the pattern of the auricular deflection: "within normal limits," "P mitrale," "P pulmonale," auricular fibrillation or auricular flutter, and "non-specific abnormality."

All cases with abnormal auricular deflections in the electrocardiogram showed some degree of anatomical changes in the atria. However, a number of cases with definite anatomical changes in the atria did not reveal any abnormalities of the P wave. Except for a few discrepancies, a close correlation was demonstrated between autopsy findings and specific electrocardiographic patterns.

MALARIA AS A FACTOR IN CARDIAC DISEASE.—J. A. Polanco Billini, M.D., Ciudad Trujillo, Dominican Republic.

Abstract in English not available.

PAROXYSMAL SUPRAVENTRICULAR TACHYCARDIA IN WHICH THE MECHANISM IS BASED ON REENTRY.—Reno R. Porter, M.D., and Samuel H. Sandifer, M.D., Richmond, Va.

The case of a 26-year-old white man is presented who had had rapid heart action ever since an attack of "rheumatic fever" twelve years previously. There was no significant incapacity from the tachycardia and no evidence of underlying heart disease. The rhythm was regular for the most part, at which times electrocardiograms showed a supraventricular tachycardia varying in rate from 140 (lying) to 160 (standing). The P waves were low in Lead I and deeply and sharply inverted in Leads II, III, and IV. On occasions the rhythm was irregular, with a rate varying between 52 and 140. Electrocardiograms demonstrated that the irregularity was due to short pauses of varying duration and frequency. These pauses occurred when an abnormal P wave failed to appear or was not followed by a QRS. The pauses ended with a normal sinus beat

which was followed: (1) by another normal sinus beat, (2) by an abnormal P wave, or (3) by an abnormal P wave and resumption of the tachycardia. Study of these tracings demonstrates that the paroxysms of tachycardia are due to a re-entry phenomenon.

The mechanisms of paroxysmal tachycardia are discussed, and the clinical significance of this particular type of tachycardia is pointed out.

SURGICAL DIVISION OF THE PATENT DUCTUS ARTERIOSUS BY MEANS OF A NEW CLAMP.—Willis J. Potts, M.D., Chicago, Ill.

The cardinal points in the diagnosis of a patent ductus arteriosus are reviewed briefly. Unless the murmur is continuous through diastole, the patient very likely does not have an uncomplicated patent ductus arteriosus.

It is generally agreed by cardiologists that the majority of patent ducti should be treated surgically. Whether the ductus should be ligated or cut and sutured has not been decided. Some feel that all ducti should be divided; others think that because of the danger of uncontrollable hemorrhage, multiple ligation is preferable. If the danger of severe hemorrhage from accidental slipping of a clamp could be eliminated, most surgeons would prefer surgical division to multiple ligation with large amounts of foreign material. Although we have ligated twenty-two patent ducti without postoperative complications, it has always been felt that surgical division is a superior procedure.

To obviate the danger of hemorrhage a new clamp has been devised. The principle of the clamp is embodied in a row of very fine teeth in the opposing jaws. The teeth of the clamp, when closed, embed themselves in the adventitia and will not slip, nor will they injure the media or intima. These clamps have been used on nine patients whose ducti have been divided and sutured. There have been no deaths and no operative or postoperative complications.

THE EFFECT OF ACUTELY INDUCED HYPOTHERMIA ON THE CIRCULATORY SYSTEM.—O. Prec, M.D., Prague, Czechoslovakia, R. Rosenman, M.D., Chicago, Ill., and K. Braun, M.D., Jersusalem, Palestine.

Cardiac output was studied by the Fick method and correlated with other changes in the circulatory system during cooling and rewarming. A direct relationship existed between body temperature and oxygen consumption, respiratory, and pulse rates. Cooling induced moderate but consistent decreases of blood pressure. In deeply anesthetized dogs, the cardiac output fell progres-·ely during cooling and initial rewarming, then increasing to only 26 per cent original values after rewarming. Substantial variations in cardiac output in ·deeply anesthetized dogs during early cooling are associated with shivering, increased pulse rate, and oxygen consumption. The cardiac output fell to 35 to 56 per cent of original values at temperature 29 to 27° centigrade. During rewarming the cardiac outputs rose more rapidly and returned almost to basal levels. The vasomotor center was very important in maintaining the blood pressure when the cardiac output decreased. There were large variations in right auricular and pulmonary arterial pressures, but no direct relationship was found between right auricular pressure and stroke volume, pulmonary arterial pressure, and work of the right heart. Associated with cooling were reversible changes in electrical systole, S-T segments, and intraventricular conduction.

FOLLOW UP OF TWENTY-ONE CASES OF SUBACUTE BACTERIAL ENDOCARDITIS AFTER TWO TO MORE THAN FOUR YEARS FOLLOWING RECOVERY.—Walter S. Priest, M.D., and Charles J. McGee, M.D., Chicago, Ill.

The twenty-one cases are divided into two groups, those (ten) surviving from three to more than four years and those (eleven) surviving from two to three years.

The following points are covered: (a) present work level, (b) incidence of cardiac failure, (c) changes in cardiac size as evidenced by x-ray, (d) development of murmurs not present during the active phase, (e) subsequent episodes of active endocarditis, and (f) relation between duration of active disease before therapy and the present level of cardiac efficiency.

In the first group are three cases of severe decrease in cardiac efficiency or reserve with episodes of cardiac failure. The cardiac efficiency in seven has remained about stationary. All show increase in the heart size as compared with that on discharge from hospital. Signs of valvular involvement not present during the active process have developed in four. Five of the seven showing the best level of cardiac efficiency had a relatively "short" duration of infection before therapy.

The status of the second group is slightly better. This is of doubtful significance since evidence of severe cardiac damage did not appear in the first group until after the third year.

At present our impression is that cardiac damage in this disease is severe in the majority of cases and that ultimate life expectancy is relatively short.

A GENERAL OUTLOOK ON CORONARY DISEASE.—Vittorio Puddu, M.D., Rome, Italy.

The recent progress in the knowledge of the different consequences of coronary disease permits a general outlook of the problem. In this way it is possible to arrange in a progressive series of continuous patterns the pathogenesis (from simple ischemia to complete occlusion) of the functional alterations and anatomical lesions of the myocardium (from the small subendocardial necrosis to massive transmural infarction), their electrophysiopathology, and their clinical pictures. The main steps of this series are: (1) effort angina; (2) prolonged decubitus angina; (3) subendocardial infarction; and (4) massive transmural infarction. From a certain point of view, it is possible to overlook the demarcation line between infarction with and without coronary occlusion: indeed, both mechanisms may overlap.

THIOURACIL IN THE TREATMENT OF HYPERTENSION.—Vittorio Puddu, M.D., and Pier Luigi Guidotti, M.D., Rome, Italy.

Hypertensive patients show a frequent increase of the basal metabolic rate and sometimes clinical signs of hyperthyroidism. For this reason the authors tried methylthiouracil in the treatment of hypertension. No other medication was given during the treatment. Up to date, fourteen patients (from 40 to 65 years of age) have been treated. They suffered from uncomplicated hypertension, with initial blood pressure levels over 220/120 and with increased basal metabolic rate. The initial daily dose of the drug of 0.60 Gm. was decreased after three to four weeks to 0.2 to 0.4 Gm. per day. Eleven patients showed definite improvement of the symptoms after the first week of treatment and some of them had a complete disappearance of their complaints some time later. The blood pressure decreased in five of these patients after two to three weeks of treatment. The systolic blood pressure was lowered by 120 mm. Hg in one single

case and by 50 mm. or more in the other four. The diastolic blood pressure was lowered by 20 to 80 millimeters.

Up to date, some of the patients have been under treatment for one year. The discontinuation of the treatment was followed by relapse of the symptoms and signs after three to four weeks. The best results were obtained in patients who showed a good response to cold, posture, and amyl nitrite tests and especially in menopausal hypertension. No signs of intolerance were noted. The studies are being continued.

HYPERTENSION AND TACHYCARDIA DUE TO CONCUSSION OF THE BRAIN.—Wilhelm Raab, M.D., Burlington, Vt.

Published in full, Am. Heart J. 37:237, 1949.

DIAGNOSTIC ELECTROCARDIOGRAPHIC CRITERIA IN LEFT VENTRICULAR HYPERTROPHY.—Pedro Rabina, M.D., Havana, Cuba.

Abstract in English not available.

ELECTROCARDIOGRAPHIC CHANGES IN TYPHOID FEVER AND THEIR REVERSIBILITY FOLLOWING NIACIN TREATMENT.—

M. Rachmilewitz, M.D., and K. Braun, M.D., Jerusalem, Palestine.

Published in full, Am. Heart J. 36:284, 1948.

POLYGRAPHIC STUDY OF CARDIAC FIBRILLATION.—Pierre Rijlant, M.D., Brussels, Belgium.

"Intrinsic" variations of the potential at twenty and sixty points of the ventricle of hearts of cats and land turtles were studied at high temperatures of about 30°C. during the ventricular fibrillation as induced by electrical excitation, and simultaneously registered by means of cathode oscillographs which could be controlled by electronic commutators. This did not enable us to demonstrate "circular contractions" in the intact heart. On the other hand, in the turtle heart, the ventricular area of which is injured, fibrillations by circular contraction are easily obtained. The number of leads used at the same time (from twenty to sixty) is not sufficient to exclude completely the possibility that a circular contraction occurred in the maintenance mechanism of the ventricular fibrillation in the intact heart. However, the sudden appearance of activity at the level of an electrode surrounded by a sufficient number of not yet activated electrodes implies that the activity so observed is determined locally; this corresponds either to a local transitory automatism or to a pseudoautomatism maintained by the delayed negativity of the preceding activation. A sufficient nition of the ventricular fibrillation of the mammalian heart can be obtained by means of a much larger number of leads. We are constructing at present vice making it possible to register 216 leads simultaneously.

SOME OF THE CARDIOVASCULAR MANIFESTATIONS OF EPILEPSY.—J. Manuel Rivero Carvallo, M.D., and Margarita Perrín Chico, M.D., Mexico, D.F., Mexico.

Abstract in English not available.

THE CARDIAC CONDUCTING SYSTEM.—Jane S. Robb, M.D., Syracuse, N. Y.

Using small hearts of various species, including man, serial sections have been cut, stained by Masson's or Mallory's technique, and photographed.

From the photographs outlines have been transferred to plastic, and portions, or all, of the system reconstructed. In the guinea pig the cardiac muscles and their conducting tissue supply have been visualized. In human fetal hearts, the studies are somewhat less completed. The transition of conducting tissue to heart muscle is known for several species. Correlation of such structure to cardiac physiology will be stressed.

THE THEBESIAN VESSELS AND OTHER SMALL VESSELS ON THE HEART AND THEIR ROLE IN NOURISHMENT AND DRAINAGE OF THE MYOCARDIUM.—Joseph T. Roberts, M.D., Little Rock, Ark.

Studies have been made on canine hearts, beating in situ as well as isolated, which indicate that the Thebesian group of vessels can serve as either drainage or nourishment channels for the myocardium of either the left or right ventricles. The direction of flow through these channels depends upon the gradient of pressure between the ventricles and the pressure in the coronary arteries.

By inspection and injection of the Thebesian openings of human hearts it is shown that these channels can be exaggerated in association with slowly progressing coronary artery stenosis.

These experiments suggested an operation, developed initially by the author, to bring a new blood supply to the ischemic myocardium. This consists of anastomosing the coronary sinus with an arterial branch of the aorta. Following such procedures, ligation of coronary arteries was not followed by the usual infarction or death, indicating that this procedure may become of value in the treatment of coronary artery disease with myocardial ischemia.

Attention is also called to the presence of extensive lymphatic circulation in the heart. Studies of the blood supply of the nerves to the heart and relating to a mechanism of cardiac pain and the absence of cardiac pain with cardiac hypertrophy are also reported.

HEART LESIONS IN SOME RHEUMATIC DISEASES NOT INCLUDING RHEUMATIC FEVER; STUDY OF 360 CASES OF RHEUMATOID ARTHRITIS AND 6 OF DIFFUSE SCLERODERMA.—Javier Robles Gil, M.D., Mexico, D.F., Mexico.

Recent histopathologic studies have shown the existence of cardiovascular lesions in rheumatoid arthritis. In this work, the presence of such lesions was investigated clinically in 360 patients. Twenty of these patients (5.5 per cent) presented endomyocardial lesions, as judged by x-ray and electrocardiographic studies. No evidence of rheumatic fever was found. The valvular and endomyocardial lesions were similar to those found in rheumatic fever, with the exception of the high incidence of aortic valvular injury and the great tolerance to the disease. Another 4.7 per cent showed endomyocardial lesions, but with the coexistence of a clinical picture of rheumatic fever. Two and one-half per cent had heart injury due to cardioangiosclerosis, hypertension, or coronary disease. In 3.3 per cent, electrocardiographic changes due to myocardial lesions were found without any other obvious cause but the rheumatoid arthritis. Nine and three-tenths per cent had slight changes in the P waves; and another 5.3 per cent had various electrocardiographic changes, probably due to hypertensive heart disease.

All six patients with diffuse scleroderma showed clinical manifestations of cardiac involvement. In three, globular heart enlargement was found, as revealed by x-ray films. In five, a progressive incomplete bundle branch block was found electrocardiographically. Very likely, eventually it will become a

complete auriculoventricular block, through involvement of both branches, as observed in one case. Two patients died of cardiac insufficiency with bradycardia.

BLOOD PRESSURE AND BODY TEMPERATURE.—Simon Rodbard, Ph.D., Chicago, Ill.

Mammals (body temperature 38°C.), including dog, man, rat, and rabbit, have normal diastolic blood pressures averaging about 80 mm. of mercury. Birds (body temperature 42° C.) including chicken, turkey, and duck, have diastolic pressures of about 120 mm. of mercury. Lowering of the body temperature of these animals produces a progressive fall in blood pressure, and rewarming is followed by a return to normal pressures. Similar temperature-pressure relationships have been demonstrated for amphibian (frog) and reptile (turtle). These pressures changes are accompanied by similar changes in heart rate, circulation rate, and cardiac output. However, the temperature-pressure relationship depends on the integrity of the central nervous system, since destruction of the brain eliminates the relationship. Further, blood pressure changes can be demonstrated by thermal stimulation of the brain in the region of the hypothalamus. The significance of these findings is discussed.

CARDIOVASCULAR CHANGES CAUSED BY ARTERIOVENOUS ANEURYSM OF THE THYROID GLAND.—Ramón A. Rojas, M.D., Tucuman, Argentina.

Abstract in English not available.

RHEUMATIC DISEASE IN THE ADULT. CLINICAL FORMS, EVOLUTION AND PATHOLOGY.—Francisco Rojas Villegas, M.D., and Manuel Bescaín, M.D., Santiago, Chile.

This work refers to the observation of 200 clinical histories of adult patients hospitalized in an adult medical service for rheumatism and 200 histories of the out-patient rheumatic dispensary. The different clinical forms, degrees of cardiac insufficiency, and the laboratory findings were considered. In the hospital cases which ended in death, the cause of death and the results of the pathological study in every case are given. In the ambulatory cases the evolution of the disease was followed for periods between five and ten years. This evolution is correlated with the type of lesion present, with the degree of radiologic and electrocardiographic alteration, and so forth. There were also studied the different preventive and control measures taken and the various treatments employed.

HE NATURE OF PAROXYSMAL TACHYCARDIA IN ANOMALOUS ATRIOVENTRICULAR EXCITATION.—Francis F. Rosenbaum, M.D., Milwaukee, Wis.

Cases of anomalous atrioventricular excitation raise many considerations not the least of which concerns the nature of the paroxysmal tachycardia which occurs in more than one-half of these patients. Two patients showing unusual features which bear importantly upon this problem have been observed. Observations were made in the first patients at the *onset* of repeated paroxysms as well as when isolated atrioventricular nodal extrasystoles were present. The ventricular complexes during these arrhythmias were of normal form but the P waves were of unusual configuration. It is postulated that the paroxysms arose from a focus in the atrioventricular node so that the manner of activation of the ventricles was normal but the path through the node to the auricles was

blocked. The ventricular impuse reached the auricle by traversing the anomalous bundle. The impulse perhaps returned to the ventricle through the normal pathway, thereby establishing a circus rhythm and initiating a paroxysm. Many isolated extrasystoles followed by retrograde stimulation of the auricles via the anomalous path failed to initiate a paroxysm, apparently because transmission through the normal conduction tissues was blocked. Other isolated extrasystoles were not accompanied by P waves, indicating that retrograde stimulation of the auricles through the accessory pathway occasionally failed. The paroxysm in this patient failed to appear if block occurred in either the normal or the anomalous conduction tissues.

In the second patient observations were made during paroxysmal tachycardia of several days' duration. The patient died suddenly two hours after the paroxysm terminated. The ventricular complexes during both the normal and the abnormal rhythms were bizarre in their configuration. After moderately large doses of quinidine were given partial heart block appeared, although the auricular tachycardia was undisturbed. It may be postulated that in those instances in which the ventricular complexes maintain their abnormal form during paroxysmal tachycardia, the impulse reaches the ventricle from the auricle via the anomalous bundle and therefore spreads over the ventricle in an abnormal manner. To establish a circus movement it must return to the auricles by passing through the normal conducting tissues in a retrograde manner. Such a circus cannot have been present in this patient because it is highly unlikely that both conduction pathways would be blocked at the same instant. It is possible that in this case supraventricular impulses reached the ventricle solely by means of the accessory bundle and that the bundle of His was not functioning. The ectopic focus or the circus rhythm responsible for the paroxysm was then entirely supraventricular in location. When the anomalous bundle became refractory, block occurred and no other functioning pathway was available whereby the impulse could reach the ventricles.

THE HEART IN RHEUMATOID ARTHRITIS; A REVIEW OF RECENT NECROPSY AND CLINICAL INVESTIGATIONS.—Edward F. Rosenberg, M.D., Chicago, Ill.

Investigations on this subject which have been conducted during the past decade are reviewed. Necropsy studies based upon an examination of more than 150 cases are summarized. The results indicated that cardiac lesions, which are indistinguishable from those found in rheumatic fever, may be encountered in more than 40 per cent of all patients with rheumatoid arthritis. The lesions encountered have varied in severity, but, in general, have been extensive, often being associated with notable scarring and deformity of valves and with severe myocardial and pericardial lesions. Often this process was responsible for severe heart failure, and frequently, the patients died as a result of the cardiac disease. The heart conditions produced by these lesions were often difficult to detect during life, even in cases where the disease had advanced to a severe degree. Even skilled clinicians often were unable to detect this form of heart disease during life.

A detailed study of the cardiac status of 150 living patients with severe rheumatoid arthritis is also reported. This investigation disclosed evidence of rheumatic heart disease in only 3.4 per cent of the total number of patients studied. The incidence of rheumatic heart disease among a control group was 2 per cent and the difference between the incidence among the patients and the control individuals did not appear to be significant.

The contrasting results from necropsy studies and from clinical examinations are discussed in relation to the possible connection between rheumatic fever and rheumatoid arthritis.

THE FAST SELF-SUSTAINED ACTIVITY OF MAMMALIAN AURICULAR MUSCLE.—A. Rosenblueth, M.D., and J. García Ramos, M.D., Mexico D.F., Mexico.

In isolated auricular appendices, fast nonstimulated discharges follow rapid stimulation after acetylcholine or carbaminoylcholine are administered. The frequency is related to that of the stimuli. Below a critical frequency of stimulation (approximately 20 per second), no automatic discharges ensue. The activity requires the presence of the choline ester. There are more discharges with larger than with smaller doses. Further injections during an episode prolong it. It is longer when acetylcholine is administered after Prostigmine, and longer for carbaminoylcholine than for acetylcholine. Atropine abolishes the phenomenon; curare does not. The discharges end suddenly. The terminal frequency (about 20 per second) is lower than the refractory period requires, for after activity ceases, stimulation elicits faster discharges, which may outlast the stimuli. The activity is usually regular, but may become irregular, as if successive impulses started at different points or several regions were discharging independently. It is probably not maintained by a circus movement; it persists in an area smaller than a square centimeter. It differs from the slow type of self-sustained activity both in frequency and in requiring the presence of an acetylcholine-like agent which inhibits the slow activity.

NORMAL VALUES OF THE ARTERIAL PRESSURE AND FREQUENCY OF ARTERIAL HYPERTENSION IN HIGH ALTITUDES.—Andres Rotta, M.D., and Artemio Miranda, M.D., Lima, Peru.

In a town of about 7,000 inhabitants and at 13,850 feet above sea level (Morococha, Peru), an investigation was conducted to detect cases of arterial hypertension. At the same time the blood pressure of 1,878 healthy individuals between 18 and 71 years of age was measured. Among this group there were fifty-three Caucasians (North Americans, Italians, Spaniards, and Peruvians), dwellers of high altitudes for many years; the rest were native Indians.

The following results were found:

1. Neither in the investigation nor in the direct examinations were cases of arterial hypertension found.
2. The systolic arterial pressure is lower in men at high altitudes than in those at sea level, (mean pressure, 108 mm. Hg); the diastolic arterial pressure is higher than at sea level, (mean pressure, 88 mm. Hg).
3. Since the few nonIndians showed no difference from the natives, either in the systolic or in the diastolic pressure, it may be concluded that the figures obtained have nothing to do with the racial characteristics and that chronic anoxia does not influence arterial pressure.

THE SYSTOLIC EXPANSION OF THE LEFT AURICLE IN MITRAL DISEASE.—D. Routier, M.D., and R. Heim de Balsac, M.D., Paris, France.

The radiologic examination of patients with mitral disease permits recognition in the most advanced cases of an expansion of the left auricular contour during ventricular systole. Radiokymography gives more precise information regarding this phenomenon, which can be observed either in the anteroposterior position when the left auricle extends to the right border of the heart, or in the right anterior oblique, left lateral, or left posterior oblique position, when the filled esophagus follows the auricular outline closely. A description is given of the radiokymogram and of the expansion observed. *Interpretation:* The left auricular distension during ventricular systole is evidence of auriculoventri-

cular regurgitation or "mitral insufficiency"; thus this physiopathological disturbance can be easily demonstrated during life. Our radiological-clinical study of the phenomenon is based upon several hundred observations.

Left auricular systolic expansion becomes more marked with marked enlargement of the left auricle and in the presence of auricular fibrillation; the more advanced the cardiac lesion, the more marked is the systolic expansion of the left auricle. The auricular expansion may or may not be present with stenosis or an apical systolic murmur of mitral insufficiency. The different possibilities can be explained by the volume of regurgitating blood. If regurgitation is slight it may set into vibration the mitral apparatus and produce a murmur but may be insufficient to distend the auricle. On the contrary, if it is marked it may distend the auricle without causing a vibration of a mitral apparatus which is more or less rigid, thickened and gapping.

The left auricular systolic expansion not only establishes the diagnosis of mitral insufficiency, but permits appreciation of the importance of that regurgitation. Thus, it is a sign of considerable importance both physiopathologically and clinically.

CARDIOVASCULAR STUDIES, WITH FOLLOW-UP RESULTS, OF THE VICTIMS OF THE TEXAS CITY DIASTER.—Arthur Ruskin, M.D., Galveston, Texas.

As previously reported (Am. J. Med. 4: 228, 1948) elevated diastolic blood pressure peaks of 95 mm. or over were found in the majority of 180 hospitalized patients injured by the Texas City explosions of April 16, 1947. This incidence of acute hypertension, occurring especially from two to twenty-eight hours following the blasts, is much higher than that found in hospitalized surgical patients or in various battle zones during World War II.

Some four to seven months following the explosions, 111 cases were reexamined for signs of cardiovascular disease. It appeared that 23 per cent of the cases showed diastolic blood pressures of 95 mm. or over, even though the lowest readings obtained following rest were so evaluated. While statistically valid comparable figures for the local general population are not available, the figure of 23 per cent was found to be statistically higher than the available figure either of industrial examinees or of insurance applicants.

Cold pressor tests were positive in 72 per cent of the postexplosion group and in 77 per cent of the follow-up group of blast victims.

In addition to the finding of hypertension as a possible result of the blast, we saw a case of severe hypertensive reaction following massive pulmonary embolism. Some cases of possible cardiac blast injuries, proved pathologically, were also encountered. Complete studies, including electrocardiographic and other examinations, throw some light upon the possible etiology of the cardiovascular abnormalities.

THE EFFECT OF VASOCONSTRICTIVE AND HYPERVOLEMIC MEASURES UPON TETRAETHYL AMMONIUM ORTHOSTATIC HYPOTENSION.—Arthur Ruskin, M.D., Galveston, Texas.

We have previously reported a finding of orthostatic hypotension in various clinical states in which vasodilation seemed to play a prominent part (Proc. Am. Fed. Clin. Res. 3: 44, 1947). Among the conditions previously and recently observed to be associated with orthostatic hypotension of various degrees have been acute and severe chronic anemias, other blood dyscrasias, hyperthyroidism, and alcoholism. Both ephedrine and desoxycorticosterone were observed by us to prevent in various degrees the orthostatic phenomona.

Tetraethyl ammonium uniformly produced orthostatic hypotension in

doses of 0.2 Gm. to 0.5 Gm. intravenously. In many cases we observed relative hypertension in the recumbent position, a phenomonon also often observed in clinical orthostatic hypotension. With a dose of 0.5 Gm. the effects were pronouncedly less or gone within thirty minutes in the majority of cases. Tetraethyl ammonium decreased the circulating blood volume (Evans blue method). While preliminary injections of paredrine (30 to 60 mg.), ephedrine (50 mg.), plasma (750 to 1,000 c.c.), and desoxycorticosterone (20 to 40 mg., plus 10 Gm. of sodium chloride) tended to increase the blood pressure, particularly in the recumbent position, subsequent tetraethyl ammonium injections produced variable results. In some cases orthostatic hypotension and tachycardia were prevented, in others they were not. Paredrine and ephedrine were effective in preventing orthostatic syncope and alleviating orthostatic hypotension in seven out of ten cases; plasma and desoxycorticosterone, in a minority of cases. The drops in circulating blood volume following tetraethyl ammonium were prevented in some cases, particulary by preliminary Paredrine and plasma. As in clinical cases, venous pressures and circulation time in the recumbent and upright positions were apparently not affected by Stamon orthostatic hypotension short of syncope.

HISTOLOGICAL CHANGES IN EXPERIMENTAL RHEUMATISM (ANAPHYLATIC).—M. SALAZAR MALLÉN, M.D., ISAAC COSTERO, M.D., AND ELENA LOZANO, Q.B.P., MEXICO, D.F., MEXICO.

Previous studies of De Gortari, Pellón, Costero and Barroso Moguel have shown that in rheumatic patients there exist encephalic lesions which give rise to clinical and anatomic manifestations described as a true rheumatic encephalopathy.

Since there are not experimental investigations related to the histologic features in the brain in experimental allergic rheumatism, the authors proceeded to sensitize rabbits with horse serum and to provoke the allergic shock through intravenous and intra-articular injections of antigen four weeks later. Seventy-two hours after the shocking dose, microscopic study of the brain revealed histologic lesions in some of the animals that could be readily compared with those already observed in cases of rheumatic encephalopathy in man.

Since none of the rabbits that were not shocked displayed these changes, it is concluded that there is experimental rheumatism. This gives support to the belief that rheumatic fever in its general pathological picture, as well as in the participation of the central nervous system, belongs to a general process of allergic sensitization, with anatomicopathologic changes, in man as well as in the animal, of the microglial component of the nervous tissue.

ATROPHY OF THE HEART; CLINICAL, PATHOLOGICAL, ELECTROCARDIOGRAPHIC CORRELATION IN 85 PROVEN CASES.—D. SANTIAGO-STEVENSON, M.D., SAN JUAN, PUERTO RICO, AND H. K. HELLERSTEIN, M.D., CLEVELAND, OHIO.

Eighty-five cases of atrophy of the heart were encountered in 2,000 consecutive autopsies. Forty-four had brown atrophy, with characteristic bipolar pigment deposition, and an average weight of 231 grams. Forty-one had simple atrophy, devoid of pigment, with an average weight of 202 grams.

The following features were noted:

1. The incidence was three times greater in women than in men, as compared with autopsy population. The average age of the brown atrophy group was 61.7 years; of the simple atrophy group, 41.8 years.

2. The ratio between heart weight and body weight was 0.42 per cent in brown atrophy and 0.48 per cent in simple atrophy (normal, 0.43 to 0.40 per cent).

3. All but one case showed extreme wasting with generalized atrophy. Major clinical diagnoses included neoplasms, chronic infections, and degenerative and metabolic diseases.

4. Important factors in production of emaciation were prolonged illness, bedfastness, fever, surgical procedures, radiation, and gastrointestinal dysfunction.

5. Clinically the atrophic heart was small or of normal size, quiet, inactive, with a faint apical or precordial short systolic murmur in 25 per cent of the cases.

6. Characteristic electrocardiograms showed progressive diminution of voltage of P, QRS, T wave, and prolongation of Q-T intervals.

7. Blood pressure fell in 76.4 per cent of cases; normotension to low levels, and hypertension to normal or hypotensive levels.

8. The small heart was able to bear its load, as shown by the low incidence of clinical heart failure. Only three patients had clinical and pathological evidence of heart failure and they had concomitant organic heart disease.

THE RECIPROCAL ACTION OF WATER, SODIUM, AND ACIDS IN RESISTANT CARDIAC EDEMA.—F. R. SCHEMM, M.D., GREAT FALLS, MONT.

Cardiac edema in advanced disease which was resistant to more usual measures was cleared in 80 per cent of 322 instances by the institution of a regimen which included a large intake of water, a moderate restriction of sodium, and small amounts of acid. In 160 instances edema did not clear with only two of the three factors of the regimen in force until the third factor was added; this was noted in from fifty to sixty instances for each of the three factors. In these observations water was given in amounts of from 1,500 to 8,000 c.c. daily, sodium was restricted to from zero to 1,200 mg. daily, and acids were given as diet or drugs, including ammonium chloride by vein, in amounts the equivalent of from zero to 16 Gm. of ammonium chloride daily.

From these observations, it seems apparent that each factor of the regime has its limitations as well as uses and the importance of their reciprocal action emerges. The most severe restriction of sodium alone, the most extreme forcing of water alone, the heaviest doses of acid alone, or the combination of any two of these, may leave untouched a resistant edema which is capable of responding dramatically to the reciprocal action of all three factors, even when each is enforced to a much less drastic degree.

MECHANISM OF AURICULAR FLUTTER AND FIBRILLATION.—D. SCHERF, M.D., NEW YORK, N. Y.

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THE EFFECT OF ERGOTAMINE PREPARATIONS ON THE ELECTROCARDIOGRAM.—D. SCHERF, M.D., AND M. SCHLACHMAN, M.D., NEW YORK, N. Y.

It has been claimed that the injection of ergotamine tartrate prevented the occurrence of postural inversion of the T waves (Nordenfelt) and that inverted T waves which may occur in the supine position in the emotionally tense individual or in neurocirculatory asthenia may be normalized by this drug (Wendkos). Both authors suggested that ergotamine tartrate could be utilized to differentiate a "functionally" inverted T wave from an inversion caused by organic disease.

Twelve patients studied by us showed significant changes in the T waves on assuming the erect position. When the experiment was repeated after the intravenous injection of ergotamine tartrate, the positional inversion of the

T waves was not prevented from recurring in eleven cases. Nineteen patients who had organically inverted T waves because of left ventricular strain and/or organic heart disease were given an intravenous injection of 0.5 mg. of either ergotamine tartrate of dihydroergotamine 45. Seven of these patients exhibited a normalization of the T waves. Five patients developed severe anginal pain which lasted from two to twelve hours, and one of these patients who had syphilitic aortitis with narrowing of the coronary ostia died twelve hours after the injection.

From these observations, it is concluded that ergotamine preparations will not invariably prevent the inversion of the T waves with a change of position of the patient. Ergotamine preparations can cause a normalization of organically inverted T waves and therefore cannot be used as a diagnostic test. Their use is dangerous in patients with coronary artery disease.

CLINICAL OBSERVATIONS WITH FAGARINE.—D. SCHERF, M.D., A. M. SILVER, M.D., AND L. D. WEINBERG, M.D., NEW YORK, N. Y.

Fourteen injections of alpha-fagarine hydrochloride were given to thirteen patients with various forms of tachycardias, auricular flutter, and auricular fibrillation. The dose varied between 0.05 and 0.12 gram. In six patients the existing arrhythmia disappeared promptly after the injection. In two patients, however, fatal ventricular fibrillation appeared; in three others dangerous multifocal ventricular extrasystoles were observed.

The observations and side reactions in all cases are discussed and the risk involved in the use of this drug is stressed.

ETIOLOGY OF AURICULAR FIBRILLATION AND THE MECHANISM OF ITS PERPETUATION.—J. G. SCHLICHTER, M.D., CHICAGO, ILL.

In this report, our experience in man and dog relating to the etiology of auricular fibrillation and the mechanism of its perpetuation is presented. Vagal stimulation and anoxia are the main etiological factors in the initiation and perpetuation of auricular fibrillation.

Vagal stimulation (mechanical and chemical) may induce auricular fibrillation. Acetylcholine injected directly into the blood stream was used in our experiments to produce chemical vagal stimulation. Moderate anoxia reduces the threshold of the auricles to the initiation of fibrillation, but does not induce this arrhythmia, per se; marked anoxia, on the other hand, increases the threshhold to fibrillation.

Anoxia of the auricles was found or produced: (1) by interference with or obstruction of its vascular supply, (2) by a decrease in the amount of oxygen carriers, (3) by a decreased oxygen content of the blood due to anoxic anoxemia, and (4) by interference with tissue respiration.

The relationship between vagal stimulation and anoxia can be plotted in a graph, and on this correlation, the cause of the perpetuation of auricular fibrilla-[illegible] can be demonstrated. The clinical implication of these findings and the [illegible]erapeutic approach to this problem are illustrated and discussed.

CARDIOVASCULAR CHANGES IN PERNICIOUS ANEMIA BEFORE AND AFTER THERAPY.—STEVEN O. SCHWARTZ, M.D., AND VLADIMIR C. FLOWERS, M.D., CHICAGO, ILL.

Ninety-two patients with pernicious anemia, ranging in age from 35 to 81 years, and equally distributed between the sexes, were studied while in hematologic relapse. Of these sixty-nine were Caucasian and twenty-three were Negro. Fifty-five complained of dyspnea, thirty-one of edema, eight had angina

pectoris, and one had intermittent claudication. Fifty-nine had systolic murmurs, distributed as follows: apical, thirty; pulmonic, ten; aortic, six; diffuse, thirteen. One patient had an apical diastolic murmur which disappeared on liver therapy (this patient had hypertension). Only eighteen patients had blood pressures over 150/90 while in relapse. Seventy-two of the patients had electrocardiograms taken; of these, forty-four were interpreted as abnormal. Fifty-seven patients had their cardiac size determined by x-ray films, thirty being found normal.

Forty-four patients were re-examined when blood values had returned to normal (three months). Of these, eleven had systolic murmurs (five apical, five aortic, one pulmonic), while nineteen had hypertension (150/90 plus). Electrocardiograms revealed abnormalities in twenty of forty-one repeat studies. Cardiac size was found to be normal in twenty-five of thirty-seven patients re-examined.

Discussion will center on the interpretation of these findings as it relates to: (1) the criteria of diagnosing cardiovascular disease in the presence of severe anemia; (2) the significance of the findings when reinterpreted on the basis of the age group involved in the study; and (3) the influence of the rapidity of onset of the anemia on the symptoms and findings.

CARDIOVASCULAR SYPHILIS IN YOUNG WHITE MALES.—John B. Schwedel, M.D., and Kona Simon, M.D., New York, N. Y.

Five hundred ninety-five syphilitic men and 786 controls were examined for auscultatory and radiographic findings to determine the incidence of aortic dilatation, aortic insufficiency, and a combination of aortic dilatation plus aortic systolic murmur and/or accentuation of the second aortic sound. The average incidence of dilated aorta was 4.2 per cent in the controls and 18 per cent in the syphilitic group. Ausculatory findings were three times as frequent in the syphilitic group without aortic dilatation and twice as frequent when the aorta was dilated. Isolated aortic insufficiency was present in 7.2 per cent.

Criteria for the diagnosis of syphilitic aortitis are suggested consisting of the presence of dilated aorta combined with significant auscultatory findings. The presence of a dilated aorta in syphilitics below the age of 40 years in the absence of aortic insufficiency, plus aortic systolic murmur or accentuation A_2, is sufficiently frequent to warrant the presumptive diagnosis.

Radiographic and fluoroscopic criteria, consisting chiefly in increased arching in the posteroanterior and left anterior oblique views, are illustrated.

PARCHMENT HEART (OSLER).—Harold N. Segall, M.D., Montreal, Canada.

In revising the sixth edition of his textbook, *The Principles and Practice of Medicine*, Osler introduced the following paragraph in the chapter on dilatation of the heart: "Dilatation may be chronic, in which case it is associated with hypertrophy. Not always, however; there is an extraordinary heart in the McGill College Museum showing a parchment-like thinning of the walls with uniform dilatation of all the chambers; in places in the right auricle and ventricle only the epicardium remains." Periodic long searches of medical literature were made in the past few years and no reference to a similar case of dilatation and generalized thinning of the myocardium could be found. This unique specimen represents a condition about which one can only speculate in considering the etiology and pathologic physiology. The records of the McGill Museum contain no clue to the patient's history in this case. It is significant that neither the heart valves nor the myocardium reveals any evidence of inflammatory disease

and that the coronary arteries are normal. The theoretical question, what degree of dilatation without hypertrophy may be reached by myocardium?, is answered by this heart more effectively than by any known experimental technique, or by any other clinical observation.

Illustrations as well as the specimen, which at first glance resembles a distended ovarian cyst, will be shown.

THE DIFFERENT TYPES OF INTRAVENTRICULAR BLOCK.—MARCEL SEGERS, M.D., BRUSSELS, BELGIUM.

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COARCTATION OF THE AORTA.—MORSE J. SHAPIRO, M.D., MINNEAPOLIS, MINN.

The subject of coarctation of the aorta has assumed practical significance now that this abnormality can be cured by surgical intervention. It seemed important, therefore, to examine the data on twenty patients observed over a period of several years. From this study the following information has been obtained:

1. The diagnosis is frequently missed.
2. Follow-up studies revealed a gradual increase in blood pressure with an accompanying increase in size of the left ventricle. The extent of erosion of the ribs, where this sign is present, increases.
3. Erosion of the ribs is not always present.
4. There is no clear correlation between rib erosion, size of the left ventricle, and degree of constriction of the aorta.
5. Collateral circulation does not develop if an accompanying patent ductus arteriosus of good size is present.
6. Enlargement of the left subclavian artery, as revealed by x-ray films, is frequently a helpful diagnostic sign.
7. Four cases observed during surgical intervention and three at postmortem examination will be discussed in detail.

BIOLOGIC STANDARDIZATION OF DIGITALIS PRODUCTS BY MEANS OF THE GUINEA PIG METHOD: COMPARISON WITH THE CAT METHOD; DIFFERENCES AND ADVANTAGES.—EUGENIO D. DA SILVA CARMO, M.D., RIO DO JANEIRO, D.F., BRAZIL.

Abstract in English not available.

MOVEMENTS AND SOUNDS OF THE HEART VALVES OF VARIOUS LABORATORY ANIMALS (MOTION PICTURE WITH SOUND RECORDINGS).—H. L. SMITH, M.D., E. J. BALDES, M.D., AND HIRAM E. ESSEX, M.D., ROCHESTER, MINN.

The hearts of various laboratory animals were perfused with oxygenated Ringer-Locke solution and were kept beating for various periods of time. Openings were made in the different chambers of the hearts and motion pictures were made of the movements of the mitral, tricuspid, aortic, and pulmonic valves. Sound recordings and electrocardiographic tracings were made at the same time.

X-RAY KYMOGRAPHY IN THE DIAGNOSIS OF PATENT DUCTUS ARTERIOSUS.—K. SHIRLEY SMITH, M.D., AND FRANKLIN G. WOOD, M.D., LONDON, ENGLAND.

In the present study x-ray kymography has been applied to the diagnosis of patent ductus arteriosus. It is considered that the radiokymographic appearances which we now present are characteristic and diagnostic of this congenital abnormality.

In kymograms of the normal heart taken by the moving grid technique the left border of the cardiac silhouette is made up of four zones which merge one with another. In patent ductus arteriosus we have observed three additional features. (1) *Vibration waves.* These are situated immediately below the aortic zone and between this and the pulmonary zone, and suggest a visual radiological counterpart of the palpable clinical thrill. (2) *Para-aortic waves.* These lie parallel to and lateral to the aortic zone and are usually faint. They differ from the faint zig-zag shadows often seen well away from the mediastinum and due simply to transmitted pulsation from the aorta or left ventricle. (3) *Exaggerated pulmonary artery waves.* These are an amplification of the waves normally seen in this zone of the pulmonary artery.

X-ray kymograms have been made in fourteen consecutive patients proved to have patent ductus arteriosus. In spite of the difficulties of radiography in young children, vibration waves were seen in all but two cases. Para-aortic waves and exaggerated pulmonary artery waves were observed less frequently, but there was only one patient in whom none of these kymographic signs was found.

CONTRIBUTION TO THE STUDY OF THE WOLFF-PARKINSON-WHITE SYNDROME BY THE INTRACAVITY LEADS.—JORGE SOBERÓN ACEVEDO, M.D., DEMETRIO SODI PALLARES, M.D., PABLO THOMSEN, M.D., BERNARDO L. FISHLEIDER, M.D., AND ANTONIO ESTANDÍA CANO, M.D., MEXICO, D.F., MEXICO.

The intracavity potential was studied in the right chambers of the heart in six patients with the Wolff-Parkinson-White syndrome. In relation to the morphology of the intracavity tracings, it was possible to classify the cases under study into two main groups. *Group A:* ventricular complexes of the QS type with a positive T wave with the electrode in the region near the pulmonary conus, and purely positive complexes with a negative T wave and with the intrinsic deflection 0.08 second after the onset when the electrode was near the tricuspid valve. *Group B:* ventricular complexes of the QS type with a positive T wave near the tricuspid valve, and purely positive complexes with a negative T and with the intrinsic deflection 0.08 seconds after the onset with the electrode near the pulmonary conus. By producing septal extrasystoles, we obtained intracavity tracings similar to those we have described.

In dogs, the experimental excitation of the ventricular septum in regions near the pulmonary conus and the tricuspid valve induced ectopic, self-sustained rhythms which at times resembled the typical pattern the syndrome produces in man.

We advance the theory that the Wolff-Parkinson-White syndrome may be caused by the presence of an anomalous atrioventricular conduction through a congenital bundle which ends in certain hyperexcitable zones of the septum situated near the pulmonary conus for the cases classified as Type A, and near the tricuspid valve for those of Type B.

EXPERIMENTAL AND CLINICAL ELECTROCARDIOGRAPHIC STUDY OF INCOMPLETE BUNDLE BRANCH BLOCK.—DEMETRIO SODI PALLARES, M.D., PABLO THOMSEN, M.D., ENNIO BARBATO, M.D., JORGE SOBERÓN ACEVEDO, M.D., BERNARDO L. FISHLEDER, M.D., AND ANTONIO ESTANDÍA CANO, M.D., MEXICO, D.F., MEXICO.

Experimental Aspect in Dog.—Transitory bundle branch block is produced by piercing the ventricular wall and pressing on the septum with a probe at the site of emergence of the branches of the bundle of His. On disappearance of the block there follow a number of different transitional complexes representing

incomplete block. A study of these transitional complexes was made with auricular and ventricular intracavity leads, and with epicardial, unipolar, and standard limb leads. Ventricular intracavity leads register a tracing of the RS type when there is complete homolateral bundle branch block. In the transitional complexes, R diminishes and S increases gradually to normal. As the block increases, epicardial leads give essentially positive complexes with initial slurring referable to abnormal septal activation, since it is synchronous with an intracavity positivity.

Clinical Electrocardiographic Aspect.—Electrocardiograms suggestive of incomplete block are shown. Q is missing in Leads I, V_L, V_5, and V_6 in left incomplete block; the slurring is as characteristic as in experimental tracings. V_1 is very characteristic in right incomplete block. rsRS type complexes are always very suggestive. The diagnostic significance of the duration of QRS is minimal.

The intraventricular study of a patient with right bundle branch block showed the following: upon swallowing, there appeared varied transitional forms of incomplete block. The complexes are of the rsrS, rsrs, and rsr (embryonic) S types. A complete set of precordial leads were also taken.

HYPERPROTEINEMIA IN HEART FAILURE.—Ben Sommers, M.D., St. Paul, Minn.

Four cases of women with chronic right heart failure over a period of years are presented. Tricuspid insufficiency was an associated lesion in all cases. Venous pressures were constantly elevated and generalized anasarca was a prominent symptom in all. Disappearance of the edema occurred spontaneously in all cases, and its disappearance was shown to be due to the development of hyperproteinemia. Osmotic pressure determinations, liver biopsies, and autopsy in two cases are presented. The etiology of cardiac edema is discussed.

A NEW STAIN FOR URINARY SEDIMENTS: ITS VALUE IN THE DIFFERENTIAL DIAGNOSIS OF HYPERTENSION.—Richard Sternheimer, M.D., and Barney I. Malbin, M.D., Chicago, Ill.

Urinary sediments may be stained by adding to the wet sediment one drop of a mixture consisting of alcoholic solutions of safranine 0 and crystalviolet in proportions of 97 parts and 3 parts, respectively. Epithelial cells, leucocytes, and casts stain readily, whereas erythrocytes either do not stain or stain only faintly. Thus, in cases of marked hematuria, the presence of epithelial cells, casts, or pyuria can be discovered easily. Recognition of hyaline, granular, epithelial, pus, and red cell casts is greatly simplified by the stain.

Two types of leucocytes may be differentiated: (1) violet staining, dead cells of uniform size and typical nuclear structure, commonly occurring in chronic cystitis, prostatitis, and vaginal discharge; and (2) faintly blue staining, usually larger cells, varying in size, containing one to four spherical nuclei. When studied with oil immersion lens, these latter leucocytes show marked Brownian movement of the cytoplasmic granules, a phenomenon described in fresh, degenerating leucocytes. Cells with Brownian granular movements are present in acute cystopyelitis, abscess of kidney or prostate, and particularly in advanced pyelonephritis. They are uniformly absent in essential hypertension not complicated by inflammatory renal disease.

On the basis of these observations, now extending over two years, a correct diagnosis of pyelonephritis in advanced cases of hypertension was made in twelve cases confirmed by autopsy. In one case, pyelonephritis superimposed upon an existing glomerulonephritis was diagnosed clinically and verified by autopsy.

STUDIES IN HEART BLOCK AND AURICULAR FIBRILLATION.—

ADOLPH SURTSHIN, M.D., AND LOUIS HORLICK, M.D., CHICAGO, ILL.

Acetylcholine injected intravenously in dogs and man may produce A-V block and auricular fibrillation. In thirty-one dogs, the minimal amount of acetylcholine necessary to produce second degree A-V block was determined. Doses of ten and twenty times this amount were then administered and the resulting arrhythmias recorded electrocardiographically. The dogs were then made anemic either by repeated bloodletting or by the exhibition of either of two hemolytic agents, acetylphenylhydrazine and *n*-propyldisulfide, and the standardizations repeated. In control standardizations the minimal standard dose was found to vary widely among different animals, but to remain relatively constant for the same animal. During each of the three types of anemia produced, the minimal standard dose fell markedly in a manner roughly paralleling the hemoglobin level. An increased tendency to fibrillate also developed during anemia. The development of auricular fibrillation was preceded in almost every instance by the development of intra-auricular block and A-V block. On a number of occasions fibrillation of the auricles clearly began with polyphasic P waves of unusual contour, suggesting that auricular re-entry is the mechanism of the genesis of auricular fibrillation. The increased sensitivity of the heart in anemia to acetylcholine (vagal stimulation) is probably due to anoxemia of the myocardium.

THE TREATMENT OF ARTERIAL HYPERTENSION WITH DIHYDROERGOCORNINE METHANESULFONATE (D.H.O. 180).—

RALPH M. TANDOWSKY, M.D., AND FRED V. CERINI, M.D., LOS ANGELES, CALIF.

Dihydroergocornine methanesulfonate, an ergot alkaloid, has known sympathicolytic properties in small dosage. Its action is based on functional blockage of sympathetic impulses to the arteriolar stream bed. Because of its cumulative properties, it must be given with caution as cumulation frequently agitates the hypertensive state. Known hypertensives appear to be hyperreactive to this alkaloid.

This preliminary report constitutes a study of an unslected group of sustained hypertensive patients whose basal, untreated blood pressure level was determined by prolonged observation prior to the administration of the alkaloid. The drug was given daily by the intravenous route in dosage ranging from 0.1 to 0.5 mg. until the ideal basal treated pressure was obtained. During this period careful clinical observation was made to determine the ideal clinical arterial pressure level for each subject. If results proved satisfactory, the drug was then administered orally in liquid form each day (0.25 to 0.5 mg.) for maintenance.

Preliminary studies seem to indicate that dihydroergocornine may prove to be a valuable adjunct in the palliative treatment of hypertension. Because of its action on the high autonomic centers in the medulla and hypothalamus, a sustained action can be depended upon, an action unlike that of the vasodepressor drugs now in common use.

THE BEHAVIOR OF THE ELECTRICAL SYSTOLE (QT INTERVAL) IN RHEUMATIC DISEASE IN CHILDREN.—Leo M. Taran, M.D., and Nelly Szilagyi, M.D., Long Island, N. Y.

In recent months there has been some discussion in the literature with regard to the value of the measurement of the electrical systole in rheumatic carditis. The prolongation of the electrical systole (Q-T interval) has been proposed as one more diagnostic sign for rheumatic carditis.

The duration of the electrical systole (Q-T interval) has been studied in a group of rheumatic children over a long period of time. It has been noted that rheumatic patients fall into five classes in regard to the duration of the Q-T interval: (1) Patients who show a normal Q-T interval which remains unaltered during the entire period of observation. (2) Patients who show a normal Q-T interval which becomes prolonged during the period of observation. (3) Those who come under observation with a prolonged Q-T interval which becomes normal. (4) Those who have a slightly prolonged Q-T interval which remains constant for long periods of time. (5) Those who have moderately prolonged Q-T interval which either remains unaltered or becomes markedly prolonged during the period of observation.

The evidence points up the observation that the prolongation of the electrical systole (Q-T interval) in rheumatic patients is a helpful diagnostic test for the presence of rheumatic carditis and in addition seems to be of important prognostic significance in following the course of acute rheumatic heart disease.

FEVER IN MYOCARDIAL INFARCTION.—Herman Tarnower, M.D., Scarsdale, N. Y.

The importance of fever in acute myocardial infarction has never been fully appreciated. No similar analysis is to be found in the literature. The basis for this study was one hundred consecutive cases of myocardial infarction. A rather typical latent period and temperature curve may be expected in over 95 per cent of those who survive the first twenty-four hours. The height and duration of the fever were analysed as to their prognostic significance, and correlated, as far as possible, with autopsy findings. Charts have been prepared to demonstrate these factors. Necropsy material served to show how little myocardial damage is required to produce a temperature elevation. Several cases illustrated the necsssity for taking rectal rather than mouth temperatures. There were several interesting clinical and electrocardiographic findings noted in the afebrile cases.

Though fever is a well-known sign in this disease, its significance has never been properly emphasized. The general practitioner rarely considers it important enough to have frequent, careful, rectal temperature recordings. He is more likely to rely solely on the electrocardiogram for confirmation of his diagnosis. Several of our cases demonstrated the fact that electrocardiographic changes may not appear for two or more weeks after the acute episode. In these instances, the history and typical temperature curve may give one confidence to persevere until electrocardiographic evidence appears.

The relative diagnostic value of the various clinical and laboratory signs employed in myocardial infarction is evaluated.

COMPLETE TRANSPOSITION OF THE AORTA AND A LEVOPOSITION OF THE PULMONARY ARTERY; CLINICAL, PHYSIOLOGICAL, AND PATHOLOGICAL FINDINGS.—Helen B. Taussig, M.D., and Richard J. Bing, M.D., Baltimore, Md.

Presented in full in this issue.

QUANTITATIVE PRODUCTION OF MYOCARDIAL NECROSIS WITH ELECTROCARDIOGRAPHIC ANALYSIS.—C. B. Taylor, M.D., O. H. Akre, M.D., and C. B. Davis, Jr., M.D., Chicago, Ill.

A new method has been used in producing myocardial lesions resembling infarcts in the hearts of dogs. The heart is exposed surgically and a hypothermal instrument is applied to the epicardium. Lesions having desired dimensions are then produced by controlled cooling of the adjacent myocardium. Lesions are reproducible in successive animals in the walls of the auricles and ventricles and in the interventricular septum. Variations such as those encountered in producing experimental infarcts by arterial ligation do not occur.

Serial electrocardiographic tracings, using standard limb leads and varied precordial leads, were obtained at intervals after the production of lesions. Animals were sacrificed after stabilization of electrocardiographic patterns. The size of each lesion in relation to cardiac size and its location were determined. Data obtained from standard limb leads and varied precordial leads were correlated with the location, age, and size of lesions. Accurate prediction as to size, location, or age of lesions produced was not possible. Precordial leads localized early anterior lesions to the right or left ventricle. Posterior ventricular lesions were distinguishable from anterior or apical ventricular lesions. Certain septal lesions gave the characteristic changes of bundle branch block.

NEW TECHNIC FOR THE RAPID PRODUCTION OF A HEART-LUNG OR HEART-LUNG-ORGAN PREPARATION.—Teodoro Texidor, M.D., Chicago, Ill.

This technique is based on the introduction of a Pyrex cannula into the descending aorta to occlude its branches. The advantages of the procedure are as follows:

Opening the thorax is practically bloodless since the intercostal vessels are interrupted. The circulation of the organ to be perfused is never interrupted; this is important, especially for the liver, where the slightest oxygen deficiency rapidly breaks down the glycogen.

The animal (dog) is first anesthetized and heparinized. The trachea is cannulated. A mid-line incision is made from xiphoid to pubis to expose the abdominal aorta. A strong cord is passed behind it one inch above the bifurcation and is loosely tied. An arterial clamp is placed one inch above the ligature and locked. The aorta is incised near the bifurcation, and the cannula is introduced upward until it reaches the clamp which is then released and the cannula rapidly pushed forward to the arch. The ligature is then quickly tied. Artificial respiration is initiated, the ribs cut, and the breastplate lifted, exposing the mediastinum and lungs. Another cord is ligated around the aorta near the arch, including the upper end of the cannula. The brachiocephalic vessels, azygos vein, and inferior cava are then ligated.

THE ELECTROCARDIOGRAM IN CONGENITAL HEART DISEASE.—Milton H. Uhley, M.D., Chicago, Ill.

A study was made correlating the electrocardiographic findings and congenital heart lesions, proved by autopsy, in a series of fifty-three cases. The records are divided into "specific" and "non-specific" pattern groups. It is pointed out that recognition of heart strain patterns is significant in identifying certain congenital lesions.

The "*specific*" *pattern group*, in infancy and early childhood, includes the following lesions: (1) Dextrocardia, which shows the classical inversion of all the components of Lead I. (2) Left coronary artery arising from the pulmonary artery, which produces a picture resembling the adult anterior wall infarction or anterior wall type of coronary insufficiency. (3) Von Gierke's Disease, which presents a picture of combined heart strain. (4) A group of lesions producing left heart strain patterns: (a) those affecting the systemic outflow tract, as aortic and subaortic stenosis; possibly congenital bicuspid aortic valve; coarctation of the aorta, adult type; congenital stenosis of the isthmus of the aorta. (Aortic atresia with underdeveloped left ventricle and aplasia of the mitral valve and ring does not belong to this group; it produces right axis shift or right heart strain. (b) Anomolies of the tricuspid valve as: tricuspid atresia with under developed right ventricle; and Ebstein's disease, congenital downward displacement of the tricuspid valve. (c) Truncus arteriosus communis. (d) Single ventricle with its variant associated anomalies.

The "*non-specific*" *patterns* presented and discussed are: (1) Right heart strain. (2) The Katz-Wachtel phenomenon, large diphasic QRS complexes in the limb leads.

THE ELECTROCARDIOGRAPHIC DIAGNOSIS OF THE DISTURBANCES OF THE HEART'S VENOUS CIRCULATION.—László Unghváry, M.D., Budapest, Hungary.

Published in full in this issue.

CIRCULATORY CHANGES PRODUCED BY ACUTE ARTERIO-VENOUS FISTULA IN DOGS.—A. Van Loo, M.D., Ghent, Belgium, and E. C. Heringman, M.D., Chicago, Ill.

Circulatory changes following production of a large A-V fistula by side to side anastomosis of the left superficial femoral vessels were studied in dogs anesthetized with chloralose and morphine.

Arterial pressures and pulse rate were measured with the Hamilton manometer. The immediate fall in pressure with associated reflex tachycardia upon opening of the fistula, and the rise in pressure with associated reflex bradycardia (Branham phenomenon) upon closing of the fistula were most marked within five to ten seconds. Thereafter, the values had a tendency to return somewhat closer to the control levels.

Pressures in the inferior vena cava remained unchanged. However, a definite rise in pulmonary artery pressures was noted when the fistula was opened.

These findings indicate the existence of compensatory mechanisms, which were studied by means of a Ludwig stromuhr introduced in the right femoral

artery and by measurement of the oxygen content of the venous blood from the head and the extremities. With fistula open, a definite reduction of blood flow in these areas was found.

Measurements of the asystolic arterial pressure gradient (as described by Wilkins and Schroeder) indicate that this reduction is due not only to a fall in systemic pressure but also to changes in vasomotor tone.

STUDY OF 150 CASES OF CHRONIC "COR PULMONALE".—MANUEL VAQUERO, M.D., JORGE ESPINO, M.D., BERNARDO FISHLEDER, M.D., AND NARNO DORBECKER, M.D., MEXICO, D.F., MEXICO.

In a study of 150 cases of chronic "cor pulmonale," their incidence among heart diseases was found to be 1.9 per cent and their etiological relation to pulmonary scleroemphysema was 100 per cent. The symptomatology is reviewed and the symptoms and signs, (dyspnea, cough, cyanosis, clubbing, murmurs, modifications of the second pulmonary sound, measurement of the circulation time, and so forth) evaluated, as well as their interrelationship. From the radiological viewpoint the importance of the Müller and Valsalva tests and the frequency of an opaque mediastinum (35 per cent), which approaches fibrosis in 12 per cent, a fact not mentioned before, is emphasized. From this study it is concluded that the diagnosis of chronic "cor pulmonale" may be made before evident signs of right ventricular hypertrophy appear and before heart failure ensues. In this respect, the features proposed by the New York Heart Association are useful only for the diagnosis of advanced cases of chronic "cor pulmonale"; many incipient ones pass unnoticed.

The cases of chronic "cor pulmonale" are divided into three groups, of which the first contains all of the features proposed as indispensable for the diagnosis of chronic "cor pulmonale."

I. *Incipient chronic "cor pulmonale."*—(a) Lung disease with pulmonary scleroemphysema and clinical signs of pulmonary hypertension. (b) Electrocardiographic: Slurred or broadened P wave in Leads II, III, and V_F; a P deviated to the right; diphasic P wave in V_1; presence of S_1Q_3 pattern. (c) Radiologic: normal heart contour or slight prominence of the pulmonary arch; large pulmonary branches; positive Müller and Valsalva tests. (d) Increased arm to lung circulation time. Normal lung to tongue circulation time.

II. *Evident Chronic "Cor Pulmonale".*—The following are added to the previous data: (a) Electrocardiographic: right axis deviation; small R in precordial leads; R in V_1 and V_2; deep S in V_5 and V_6; negative T wave in V_1 and V_2. (b) Radiologic: right auricular and right ventricular hypertrophy.

III. *Chronic "Cor Pulmonale" With Heart Failure.*—In addition to the previous findings, those of congestive heart failure are superimposed with the presence of fine, moist râles at the lung bases.

CLINICAL-ELECTROCARDIOGRAPHIC SYNDROME OF ACUTE OR SUB-ACUTE CORONARY OBSTRUCTION.—R. VEDOYA, M.D., AND J. GONZÁLEZ VIDELA, M.D., BUENOS AIRES, ARGENTINA.

Clinical cases of acute or subacute coronary obstruction are described which do not lead to a myocardial infarct as can be ascertained by the absence of fever, leucocytosis, or accelerated sedimentation rate.

The electrocardiographic picture is different from that observed in myocardial infarction both in appearance and evolution; its contour, however, shows great similarity to certain records obtained in patients with angina pectoris after the exercise test, as well as to the modifications induced experimentally by coronary obstruction or transitory total obstruction maintained during a shorter period than that necessary to cause necrosis of the myocardium. The electrocardiographic disturbances persist for days or weeks and the authors discuss the cause of persistence that is longer than that observed in certain experiments in the dog or in the human electrocardiogram during the effort test. The preexistant electrocardiographic picture does not allow prediction as to whether it will assume the Q_1T_1 or Q_3T_3 type when the myocardial infarct is finally developed.

Attention is called to the importance of this clinical-electrocardiographic syndrome and to the necessity of differentiating it from the classic syndrome of angina of effort and from that of myocardial infarct.

INTERAURICULAR COMMUNICATION; A STUDY OF 20 CASES.—MARIO VIZCAÍNO, M.D., MANUEL VAQUERO, M.D., AND RUBÉN PELLÓN ISLAS, M.D., MEXICO, D.F., MEXICO.

Twenty cases of interauricular communication, proved by cardiac catheterization (thirteen) and by post-mortem studies (seven) are presented. Thirteen are cases of the so-called "Lutembacher syndrome"; the remaining seven are isolated interauricular communications.

Clinical signs are considered significant when associated with radiologic and electrocardiographic data. These clinical signs are: systolic murmur over the pulmonary area, with or without accompanying thrill, and a loud second pulmonic sound and a palpable pulmonary closure. The systolic murmur is considered to originate in the vessel itself and not in the septal defect.

The x-ray examination shows: enlargement of the right chambers of the heart with increased pulsation, dilatation and hyperpulsation of the pulmonary artery and its branches, and a relatively small aorta with decreased pulsation. The angiocardiographic studies exhibit either simultaneous filling of all cavities at the end of the injection, or a later filling of the right auricle when the left one is just being filled, the latter being due to a left to right shunt.

The electrocardiogram, very characteristic in such cases, shows complete or incomplete right bundle branch block.

A pathognomonic sign is given by cardiac catheterization when the catheter enters the left auricle through the interauricular septal defect or, at least, when there is an appreciable difference between the mean oxygen content of the blood from the vena cava and that from the right auricle.

The pathological physiology of such a defect is discussed, the pulmonary circulation and its relation to the systemic being considered. The differential diagnosis between isolated interauricular septal defects and the so-called Lutembacher syndrome are commented upon.

THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS WITH PENICILLIN IN OIL AND BEESWAX.—ITALO F. VOLINI, M.D., WILLIAM S. HOFFMAN, M.D., AND JAMES R. HUGHES, M.D., CHICAGO, ILL.

Eleven patients with clinical signs of subacute bacterial endocarditis, with bacteriologic confirmation in all but one, were treated with one daily dose of parenteral penicillin. Eight of these, harboring streptococci with an in vitro

sensitivity of less than 1.6 units of penicillin per milliliter, were treated with daily intramuscular injections of 2 ml. of hard Romansky formula penicillin (crystalline potassium penicillin in peanut oil and beeswax) totaling 600,000 units.

The average sensitivity of the organisms isolated in the first eight patients was 0.3954 units of penicillin per milliliter. Therapeutic blood levels proved to be adequate in all patients as compared with the sensitivity of the invading organisms. The average at two hours on single daily doses of 600,000 units was 2.27 and at twenty-four hours, 0.449 units per cubic centimeter.

The results obtained were satisfactory in eight of the eleven patients studied. There were no reactions to the many injections.

Provided the invading organisms are not too penicillin resistant, this form of therapy proved to be more satisfactory than the currently popular multiple injection or continuous intravenous routines, providing less inconvenience and discomfort to the patients and facilitating a convenient and time-saving procedure for the nursing and medical attendants.

CORONARY FLOW IN AURICULAR AND VENTRICULAR TACHYCARDIAS.—René Wégria, M.D., and Richard P. Keating, M.D., New York, N. Y.

When paroxysmal auricular tachycardia is electrically induced in anesthetized dogs, there is an immediate drop in coronary flow and mean blood pressure; then both return to their control levels. When the auricular rate is not too high, the flow may even rise above its control value. As the rate of tachycardia increases, the decrease of flow and blood pressure is more marked and more prolonged, and occasionally flow and blood pressure remain below their control values. When tachycardia stops, flow and pressure increase above control value as well as above their value during tachycardia. The higher the rate of tachycardia, the higher the increase in flow and blood pressure. Generally the blood pressure returns to normal before the flow.

In ventricular tachycardia, essentially the same phenomena are observed, with a few distinct quantitative differences, the main one being that blood pressure and coronary flow decrease more in ventricular tachycardia than in auricular tachycardia of the same rate.

The intimate mechanisms of the phenomena observed and their clinical implications are discussed.

STUDIES ON THE COMBINED EFFECTS OF CEDILANID AND QUINIDINE.—S. A. Weisman, M.D., Los Angeles, Calif.

Digitalis and quinidine are two drugs commonly used in the treatment of heart disease. Studies that confirm previous findings or offer any additional information on the action of these drugs are perhaps warranted.

The purpose of this study was to investigate: (1) The pharmacologic action of digitalis and quinidine when given consecutively at varying time intervals and when both drugs are administered together. (2) The effect of quindine on respiration.

Electrocardiographic and kymographic studies were carried out on cats. The result of this study indicates:

(1) Cedilanid and quinidine are not synergistic in their action on the heart. (2) The pharmacologic effect on the heart appears more favorable when the two drugs are given together than when Cedilanid is first given and later followed by quinidine. (3) Fatal effects occasionally attributed to the action of quinidine are perhaps frequently due to its depressent effect on the respiration rather than to its toxic effect on the heart.

It is to be emphasized that clinically it is important that quinidine be started in small doses, and that the size and frequency of the doses be gradually increased. This method may avoid some of the toxic effects attributed to the drug.

THE GRAPHIC REGISTRATION OF BASAL DIASTOLIC MURMURS.—BERTRAND G. WELLS, M.D., LONDON, ENGLAND, MAURICE RAPPAPORT, E.E., BOSTON, MASS., AND HOWARD B. SPRAGUE, M.D., BOSTON, MASS.

To be published in full in this issue.

THE ROLE OF IMPAIRED RENAL HEMODYNAMICS IN THE UNRESPONSIVENESS TO MERCURIAL DIURETICS OBSERVED IN SEVERE CHRONIC CONGESTIVE FAILURE.—RAYMOND E. WESTON, M.D., DORIS J. W. ESCHER, M.D., AND LOUIS LEITER, M.D., NEW YORK, N. Y.

Despite the fact that many patients may respond satisfactorily to mercurial diuretics for years, the unresponsiveness to these diuretics which frequently develops in severe chronic congestive failure generally has been attributed to increased tubular resistance to mercury. The present paper is an attempt to analyze this phenomenon as a late manifestation of impaired renal hemodynamics, the importance of which in the salt retention of chronic cardiac congestive failure recently has received new emphasis.

The subjects who no longer responded satisfactorily to mercurial diuretics were all edematous cardiacs except one nonedematous hypertensive in whom a very low glomerular filtration rate was produced by the Kempner rice diet. Renal clearances of mannitol (glomerular filtration rate), para-amino hippuric acid, (renal plasma flow), sodium, and chloride were determined before and after administration of Mercuzanthin, and again, following the mercurial, when the rates of sodium and chloride filtration had been increased by the rapid intravenous administration of Aminophyllin (0.48 to 0.72 Gm.) or the continuous infusion of 4.5 per cent sodium chloride (at times, plus molar sodium lactate).

After Mercuzanthin administration, there was no significant increase in the very low later and salt excretion rates which prevailed during the control periods. However, following the Mercuzanthin, if the filtration of sodium and chloride was sufficiently increased by the aminophylline or the concentrated salt solution, there was a marked increase in urinary salt and water outputs, which, at times, approached values observed in cardiacs considered responsive to mercurials.

It is concluded that the previous failure of these patients to respond to mercurial diuretics resulted not from the usually postulated renal tubular resistance to mercury, but from the marked decrease in filtration of sodium and chloride in the presence of normal tubular function. The significance of these data will be discussed with particular emphasis on the relationships between imparied renal hemodynamics, glomerular and tubular function, and salt retention in chronic congestive failure.

ON THE POSSIBILITY OF CONSTRUCTING AN EINTHOVEN TRIANGLE FOR A GIVEN SUBJECT.—Frank N. Wilson, M.D., J. Marion Bryant, M.D., and Franklin D. Johnston, M.D., Ann Arbor, Mich.

Published in full in this issue.

CARDIAC FUNCTION AND RECOVERY TIME.—Max Winternitz, M.D., Trutnov, Czechoslovakia.

Ventricular extrasystoles due to digitalis or strophanthin are characterized by their varying electrocardiographic contour. The first tracing to be shown was obtained on a patient with mitral stenosis, strophanthin intoxication, auricular fibrillation, and bigeminal rhythm with fixed coupling. Whenever the postextrasystolic pause is shorter than 0.78 second, the next extrasystole resembles the experimental monocardiogram of one ventricle, whereas with maximal postextrasystolic pauses the next extrasystoles assume the contour of incomplete bundle branch block of the opposite type.

The second record, an instance of intermittent bigeminal rhythm, demonstrates a similar and more frequent phenomenon. Here, the actual occurrence of extrasystoles is determined by the length of the preceding pause; only the beats occurring after a long pause are followed by extrasystoles. To explain these phenomena we assume in the first case partial and in the second case complete exit block for the extrasystolic impulse.

The third electrocardiogram, an example of electrical alternans, obtained on a soldier with effort syndrome, demonstrates a different aspect of the recovery problem. At a cardiac rate up to 80 the electrocardiogram appears normal; at a rate above 120 the T wave becomes abnormal; at intermediate rates there is alternation of normal and abnormal T waves.

The last electrocardiogram, obtained on a patient with recent myocardial infarction, shows, in strict dependance upon rate, the appearance of left bundle branch block which completely obscures the evidence of myocardial infarction, present at lower rates.

THE AXIS-THEORY OF THE ELECTROCARDIOGRAM.—Imre Zarday, M.D., Budapest, Hungary.

The individual deflections of the electrocardiogram are, generally, the rectangular projections on the limb leads of the heart vector. This latter can easily be constructed if one knows the heights of the deflections in two leads. Thus, a P axis (vector) is related to auricular activity, the R axis is synchronous with the propagation of the excitation wave along the specific pathways, the S axis seems to be the expression of the spread of excitation through the muscular walls of the heart, and the T axis corresponds to the regression of the state of excitation. The physiologic basis of the Q deflection can not as yet be determined. The R axis deviates to the left both in cases of left hypertrophy and transverse heart. Differentiation between these two conditions can easily be carried out on the basis of the S axis. A similar analysis can be made concerning right axis deviation. The angle formed by the R and T axes gives evidence of myocardial disease and its site. Theoretical suppositions find corroboration in clinical data and in vectocardiography. This concept of electrocardiography permits a deeper insight into the physiologic processes underlying the individual electrocardiographic deflections.

THE U WAVE.—R. ZUCKERMANN, M.D., AND A. ESTANDÍA CANO, M.D., MEXICO, D.F., MEXICO.

The positivity of the U wave in Lead V_1 increases with the Valsalva test and decreases with the Müller test; both of these changes are evident during the initial phase. In precordial leads inversion of the U wave is observed during the ischemic phase of anterior infarcts and positivity is observed during the same phase in posterior infarcts. In esophageal leads positive U waves are seen at low ventricular levels and negative ones at low auricular levels. When septal extrasystoles are present, they are registered after the U wave and during the U-R interval (supposed septal refractory period).

These observations, together with those already postulated (that cases with unilateral increase in the ventricular pressure cause a shift of A-U toward the ventricle with lower pressure), are in accord with the hypothesis that the U wave corresponds to a delayed septal repolarization as a result of the bilateral pressure the septum is subjected to. The repolarization would take place during the phase of isometric relaxation early in diastole with its attendant fall of intraventricular pressure; the direction of the repolarization would be from the right anterosuperior to the left posterosuperior region of the septum.

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Original Communications

THE EFFECT OF A LOW FAT DIET ON THE SPONTANEOUSLY OCCURRING ARTERIOSCLEROSIS OF THE CHICKEN

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THERE has long been a belief that dietary factors, particularly fats and cholesterol, may play an important role in the pathogenesis of atherosclerosis. Aschoff, on the basis of his studies on human and animal material, was of the opinion that some degree of lipemia was always necessary if atherosclerosis were to appear. He said, "From plasma of low cholesterol content no deposition of lipoids will occur even though the mechanical conditions *are favorable*."[1] The view that hypercholesterolemia and hyperlipemia are essential for the development of atherosclerosis was fortified considerably by the experimental production of atherosclerosis in numerous animal species by cholesterol feeding.[2,3,4] It has also received added support from clinical correlations of the diet and the incidence of atherosclerosis among different ethnic groups in widely different areas of the world. Rosenthal[5] and Hueper,[6] who have reviewed this subject, concluded that wherever and whenever fat constituted a large proportion of the diet, marked arteriosclerosis was prevalent. Wilens[7] has noted a correlation between the state of nutrition and the incidence and severity of atherosclerosis. Thus, overnutrition is associated with a higher incidence of atherosclerosis than is undernutrition.

Observation on the treatment of diabetics in recent years, with a low calorie, low fat, high carbohydrate diet, tends to indicate that with this regime the incidence of arteriosclerosis has declined, as compared with the incidence under

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the high fat diets previously employed.[9] In his recent survey of this aspect of diabetes, Root stated, "We believe that the chief cause of premature development of arteriosclerosis in diabetics, save for advancing age, is an excess of fat in the body (obesity), in the diet, and in the blood, due to lack of control of the diabetes."[10]

Recently Moreton[11] has advanced the theory that atherosclerosis is the result of the ingestion of many fatty meals over the course of a lifetime. On the basis of the foregoing suggestive evidence, some clinicians have been advocating the use of a low fat, low cholesterol diet in patients with atherosclerosis.

There is, however, no clear-cut clinical evidence that the data outlined are anything but suggestive. The difficulty has been in setting up adequately controlled experiments in man or in animals. The work of Fox[12] and of Dauber[13] has provided us with an experimental animal in which this problem may perhaps be elucidated. The chicken, in common with other members of the class *Aves*, develops atherosclerosis of the elastic and muscular arteries at a fairly early chronological age. By the age of one and one-half years more than 50 per cent of chickens show arterial lesions which resemble human atherosclerosis in many respects. In this preliminary experiment we have attempted to evaluate the effect of removing fat and cholesterol from the diet on the development of the spontaneous vascular changes in the chicken.

METHODS

White leghorn cockerels approximately 6 to 10 weeks of age at the commencement of the experiment were divided into two groups. Group 1 consisted of sixteen chickens which received a diet of chick starter mash and water freely. Group 2 consisted of fourteen chickens which received a diet containing the same chick starter mash from which the cholesterol and fat had been removed by repeated alcohol ether extractions.* The diets were made approximately isocaloric by the addition of sucrose, and vitamins removed in the extraction procedure were replaced. Vitamins A, D, and E† were given in highly concentrated form in a few drops of cottonseed oil, and vitamin B was given in the form of bakers' yeast. The exact composition of the diets is detailed in Table I. The diet of Group 2 was a low fat diet containing essentially no cholesterol and approximately 0.1 to 0.3 per cent of fat, as compared with 3.0 to 5.0 per cent of fat in the control diet. It has been shown previously that chickens will remain healthy and grow on this fat extracted diet.[14]

Animals died or were sacrificed at intervals up to sixty-three weeks of feeding. The hearts and aortas were dissected out en bloc and carefully examined for evidence of atherosclerosis. Lesions, if any, were recorded on special forms and graded grossly 0 to 4 according to criteria previously described.[8] Sections were taken for microscopic examination from the aortas of all the birds. The chickens were bled from the alar vein at three- to four-week intervals and the total blood cholesterol was determined by the method of Schoenheimer and

*We are grateful to Armour Laboratories for extracting large quantities of mash.
†We are grateful to Lederle, Inc., for our vitamin supply.

TABLE I. COMPOSITION OF DIETS

Chick Starter Mash		Fat Extracted Chick Starter Mash	
Crude protein	18.0%	Crude protein	18.0%
Crude fat	3–5%	Crude fat	0.1–0.3%
Carbohydrate	54%	Carbohydrate	54%
Cholesterol	0.06%	Sucrose*	5%
		Cholesterol	0.0%
Vitamin		*Vitamin*	
A	1,800 USP per lb.	A	1,200 USP per lb.
D_3	360 AOAC units per lb.	D_3	180 AOAC units per lb.
		E	30 mg. per lb.
		B (brewers' yeast)	9.08 Gm. per lb.

Ingredients
Ground corn, ground oats, ground wheat, wheat bran, wheat middlings, alfalfa meal, meat and bone scraps, dried buttermilk, soy bean oil meal, steamed bone meal, calcium carbonate from limestone, salt 1.0 per cent, manganese sulfate 0.025 per cent, and potassium iodide, a trace.

*Added to mash.

Sperry.[15] Prior to the conclusion of the experiment at sixty-three weeks, 20 c.c. of blood was withdrawn under oil and a complete lipid analysis was done. The animals were sacrificed with Nembutal and the carcasses were defeathered and disemboweled. The intestines were opened and washed free of their contents. The livers were dissected free. The carcasses and viscera (except the liver), considered together as "carcass" in subsequent procedures; and the livers, were weighed wet, and then the carcasses were ground in an electric meat grinder until homogeneous mixtures were produced. The livers were minced and homogeneous samples taken. Blood and tissue lipids were determined on aliquots of alcohol-ether extract prepared according to the method of Man and Gildea[16] for blood, modified after Bloor[17] for tissues. For total fat, the aliquots of alcohol-ether extract were evaporated to dryness on a constant temperature, low-heat hot plate, and the lipid residue was re-extracted with petroleum ether, transferred quantitatively with repeated washings to tared beakers, evaporated to dryness, cooled to room temperature in a desiccator, and weighed. Fatty acids were determined on aliquots of alcohol-ether extract according to the method of Man and Gildea.[16] Blood lipid phosphorus was determined on aliquots of the alcohol-ether extract according to the Man and Peters[18] modification of the method of Fiske and Subbarow.[19] Total and free cholesterol were determined according to the method of Schoenheimer and Sperry[15] on alcohol-acetone extracts of blood and tissues prepared similarly to the alcohol-ether extracts. All determinations were carried out in duplicate.

RESULTS

Vascular Lesions.—In Table III we have arranged the data to allow comparison between the two groups on the basis of duration of the feeding periods. It is evident that up to twenty-five weeks of feeding, none of the chickens on the low fat diet developed gross lesions of the aorta, while three out of five of the control chickens did. Between twenty-five and fifty weeks, two out of five of the

low fat group developed lesions, while five out of seven of the control group were similarly affected. Between fifty and sixty-three weeks, three out of four of the low fat chickens, and two out of four of the control group developed lesions of the aorta. Therefore, when the element of time is considered it appears that lesions developed sooner in the control birds than in birds fed a low fat diet. However, with prolongation of the feeding period beyond fifty weeks, the incidence in both groups became roughly the same. Taking the groups as a whole, gross lesions were seen in five of fourteen chickens on the low fat diet (35 per cent) and in ten of the sixteen chickens on the control diet (63 per cent). Table II illustrates clearly that the severity of the lesions was considerably greater in the control group than in the low fat group. It also indicates that whereas there was a difference in the incidence of gross lesions between the two groups, the incidence of microscopic lesions was about the same in both groups.

Table II. Summary of Gross and Microscopic Grading of Lesions of the Aorta

Control Group					Low Fat Group				
No.	Gross		Microscopic		No.	Gross		Microscopic	
	Thorac.	Abd.	Thorac.	Abd.		Thorac.	Abd.	Thorac.	Abd.
154	0	0	—	—	86	0	0	—	0
92	0	0	0	0	72	0	0	0	+
157	0	1–2	0	++	71	0	0	—	—
96	0	1–2	0	+	74	0	0	0	0
91	0	1	0	+	84	0	0	0	0
99	0	0	0	+	75	0	¼-½	0	++
97	0	1	0	+	77	0	0	0	+
150	0	0	0	—	80	½	0	0	+
89	1–2	1	+	0	83	0	0	0	+
152	0	1	0	+	81	0	0	0	++
98	0	2	0	+++					
100	0	1	0	+++					
93	0	1	0	++	78	0	1	0	+++
90	0	1–2	0	++	79	0	0	0	0
99	0	0	0	+	76	½	0	0	0
94	0	0	0	+	82	¼	0	++	++

In our cockerels the lesions were largely limited to the muscular aorta, which consisted of the descending thoracic and abdominal portions of the aorta. The abdominal aorta was by far the most common site of change. In most instances the intima of the abdominal aorta was elevated by a longitudinal white or yellow ridgelike thickening in the interrenal area (Fig. 1). The white ridgelike area occurred with equal frequency in both groups, but the incidence of grossly yellow lesions was much higher in the control group than in the low fat group. One in the control group showed thickening of the intima of the ascending portion the thoracic aorta and distinct yellow nodular lesions of the brachiocephalic vessels. Two birds of the low fat group showed bright yellow unraised areas

in the arch of the aorta. A third showed a slightly raised, scaly white plaque in the arch of the aorta.

TABLE III. INCIDENCE OF GROSS LESIONS

DURATION OF FEEDING PERIOD (WEEKS)	CONTROL GROUP			LOW FAT GROUP		
	NO. OF CHICKENS	NO. WITH LESIONS	PER CENT WITH LESIONS	NO. OF CHICKENS	NO. WITH LESIONS	PER CENT WITH LESIONS
0–25	5	3	60	5	0	0
26–50	7	5	71	5	2	40
51–63	4	2	50	4	3	75
Total	16	10	63	14	5	35

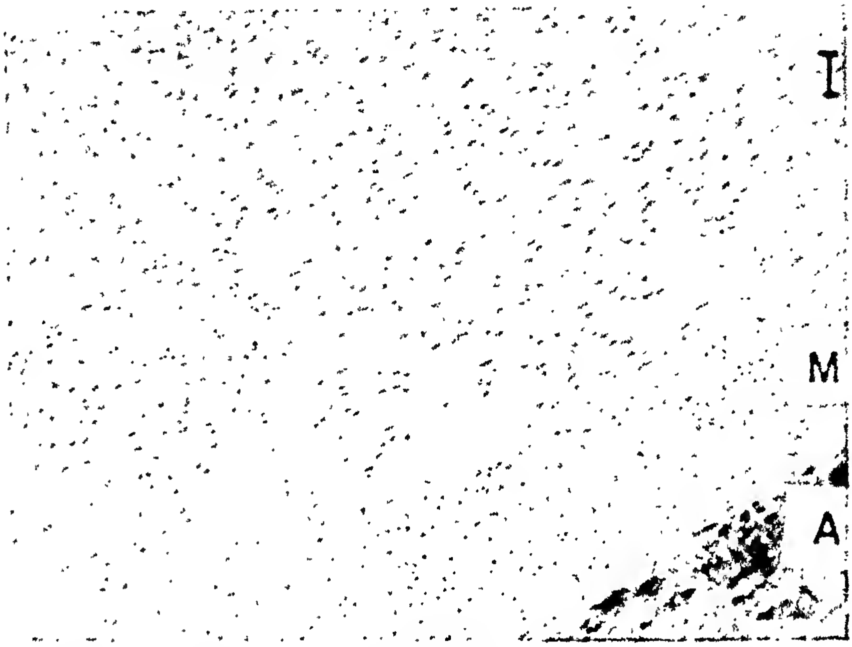
Fig. 1.—Photograph of the muscular aorta of two chickens, that is, the descending portion of thoracic and abdominal aorta. Note prominent ridgelike elevation in interrenal area. This is the characteristic location of the "spontaneous" lesions.

*Microscopic Pathology.**—In both groups the lesions of the muscular aorta, as seen in sections stained with hematoxylin-eosin, and in frozen sections stained with Sudan IV, were essentially similar and were identical with those previously described by Dauber and Katz.[3] The intima was thickened to a varying degree by fibrocellular connective tissue which was young and cellular in regions of little proliferation and also at the surface of large plaques. The deeper portions of the placques were composed of dense acellular connective tissue with areas of hyaline degeneration of the collagen and with fusiform cholesterol crystal clefts and calcific granules. In some cases the deeper layers of the fibrous plaques

*We are indebted to Dr. O. Saphir of the Department of Pathology for checking random specimens with us.

contained large, pale foam cells. Fat stains showed varying quantities of lipids in the depths of the thickened intima and also in the adjacent tissue of the media. Figs. 2 and 3 illustrate the typical appearance of the spontaneous lesions stained with hematoxylin-eosin and in frozen section. These lesions are typical atheromas.

Fig. 2.



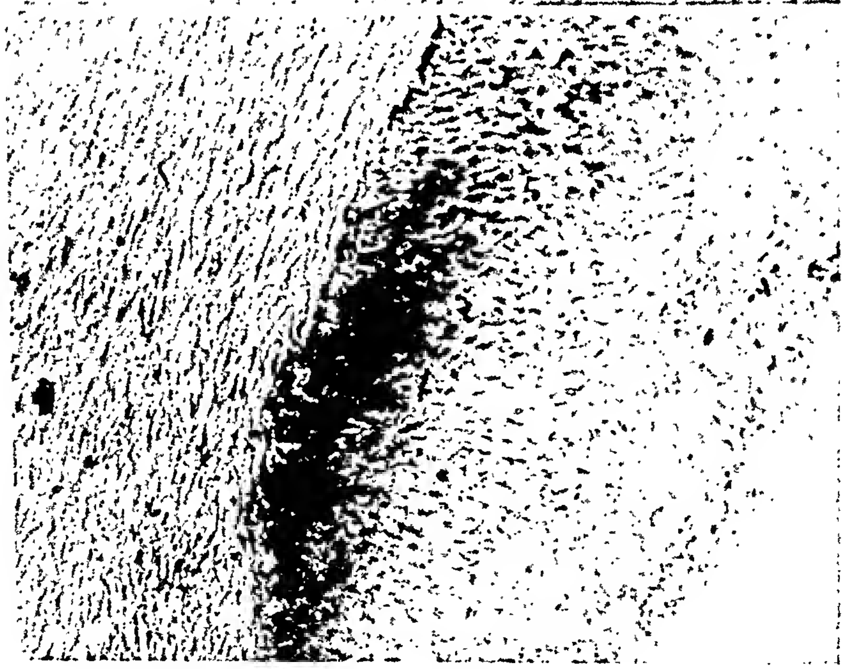


Fig. 3.

Fig. 2.—Hematoxylin-eosin stained paraffin sections (× 160) from control bird fed ordinary mash for fifty-plus weeks. There is marked thickening of the intima (*I*) which is fibrocellular in nature. Depths of plaque show more collagen, and hyalinization of the connective tissue has occurred. Area next to media (*M*) shows mucoid degeneration and is the site of fat deposition. *A* is adventitia.

Fig. 3.—Frozen section (× 320) stained with Sudan IV from control bird fed ordinary mash for fifty-plus weeks. Note marked thickening of intima, largely cellular in nature. There is a heavy deposit of sudanophilic material in the depths of the intima, adjacent to the media.

One of the chickens from the low fat group (No. 78) showed marked involvement of the abdominal aorta on gross inspection. Microscopically there was typical intimal involvement with sudanophil material in the depths of the plaque along the intimal medial boundary and scattered heavily throughout the media. The entire vessel wall was infiltrated with mononuclear cells. This was not seen in any of the other birds.

The lesions of the elastic thoracic aorta differed from those of the abdominal aorta. Thus, in No. 82 of the low fat group, the lesion consisted almost entirely of medial involvement. There was deposition of large and small fat droplets in the ground substance of the media between essentially normal looking tissues and in areas of apparent degeneration of muscle tissue. There was negligible involvement of the intima.

Unfortunately, the series was too small to allow us to judge whether there was a quantitative difference in the amount of fat in the lesions of the control and low fat series.

It is concluded, therefore, that gross lesions were more frequent and severe in the control group than in the low fat group. Microscopically atheromatosis was present in both groups and the structure of the lesions was essentially similar.

Blood and Tissue Lipid Determinations.—The results are summarized in Table IV. The average live weights of the two groups at the conclusion of the experiment were almost identical, the low fat group averaging 1,848 grams and the control group 1,857 grams. Likewise, the group averages of liver weights were similar, being 19.6 grams for the low fat group and 22.9 grams for the control group. These data, plus the condition of the animals on inspection and

TABLE IV. LIPID ANALYSES: COMPOSITE CHART OF AVERAGE VALUES FOR TWO GROUPS OF CHICKENS

	LIPID P (MG. %)	PHOSPHOLIPID (MG. %)*	TOTAL CHOLESTEROL (MG. %)	FREE CHOLESTEROL (MG. %)	CHOLESTEROL ESTERS (MG. %)	TOTAL FATTY ACIDS (MG. %)†
Blood Lipids: Control group	6.02	156.5	98	27	71	196
Blood Lipids: Low fat group	6.71	174.4	125	43	82	243
Liver Lipids: Control group			307	272	35	
Liver Lipids: Low fat group			357	297	60	
Carcass Lipids: Control group			110	100	10	
Carcass Lipids: Low fat group			107	97	10	

*Expressed as lecithin: lipid P × 26.
†Expressed as palmitic acid.

the lack of pathological findings at necropsy, confirm that the low fat diet used was adequate nutritionally and permitted normal growth and development.

The blood lipid analyses reveal a suggestive, slight (10 to 20 per cent) elevation of each of the lipid fractions of the low fat group over those of the control group. It is to be noted that throughout the experiment the periodic routine blood cholesterol determinations revealed a consistent (10 to 20 per cent) increase in this constituent for the low fat group (Fig. 4).

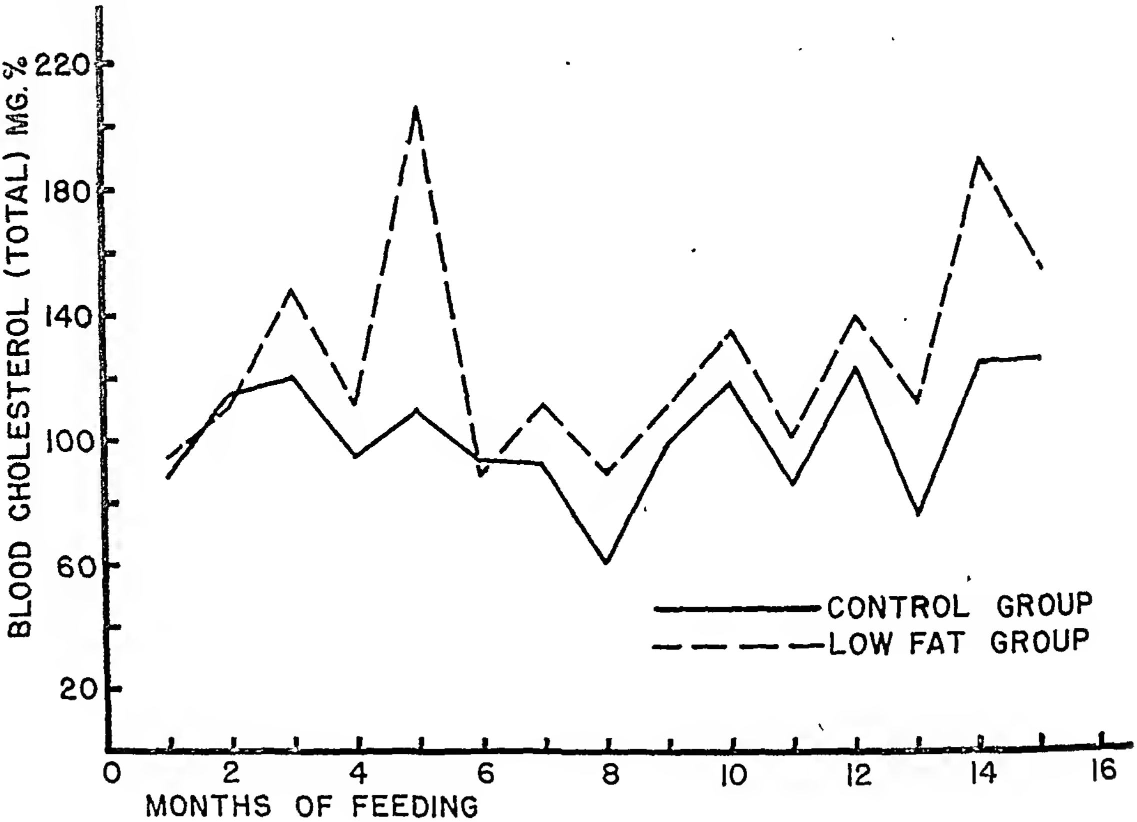


Fig. 4.—Average blood cholesterol levels of control and low fat group of chickens.

The liver cholesterols of the two groups were essentially similar, with certain small differences which are not significant statistically because of the small number of birds analyzed and the range of the values.

The lipid constituents of the carcass showed no significant variations between the two groups.

TABLE V. FECAL LIPID EXCRETION

	TOTAL FAT (MG. %)	TOTAL FAT (24 HOURS)	FATTY ACIDS (MG. %)	FATTY ACIDS (24 HOURS)	LIPID P (MG. %)
Low fat group (4 chicks)	500	1,490 mg.	358	1,070 mg.	trace
Control group (4 chicks)	595	1,465 mg.	361	885 mg.	trace

Studies of the fecal lipids revealed that with respect to the per cent of lipid in the feces and the total twenty-four hour lipid excretion, the two groups were remarkably similar (Table V).

Our data on chicken lipid analyses are similar to those reported in the literature by other workers.[20]

DISCUSSION

Our results indicate that the restriction of fat and cholesterol in the diet of the chicken to very low levels does not prevent the development of spontaneous atherosclerosis in that species. There is, however, suggestive evidence that the severity of the lesions is less when fat is restricted. Thus, the number of gross yellow lesions was higher in the control group than in the low fat group, whereas the number of lesions visible under the microscope was about the same in both groups of birds.

The theoretical implication of this is twofold. First, it negates the necessity for invoking exogenous lipid and hyperlipemia in the pathogenesis of the naturally occurring lesions, and second, it indicates that although exogenous lipid is not essential to atherosclerogenesis it nevertheless tends to accelerate its progress and to increase its severity.

It would seem then that the so-called "endogenous lipid level" is adequate to permit the process of atherosclerogenesis to proceed. This is of great interest because it brings the experimental aspect of atherosclerosis into line with prevailing clinical impressions. Most instances of human atherosclerosis occur in the presence of normal lipid levels in the blood. Cholesterol feeding experiments have failed to supply fundamental clues to the nature of human atherosclerosis because they represent an abnormal and highly exaggerated condition which has no true parallel in human atherosclerosis, with the possible exception of xanthomatosis with hypercholesterolemia and some cases of diabetes. The theories of Anitschkow[2] and Aschoff,[1] of Leary,[21] and latterly of Moreton[11] all invoke a temporary or permanent lipemia or chylomicronemia as the precursor of the atherosclerosis. Certainly the evidence afforded by our experiments suggests that this view will have to be amended. We do not wish to deny the role of the lipids in arteriosclerosis. We merely wish to suggest that the "endogenous" or normal lipid concentration of the blood is adequate for the exercise of that role. When more lipid is made available, the influence of the lipids probably results in the acceleration and aggravation of the sclerotogenic process.

Our data on both blood and tissue lipids of chickens maintained for sixty-three weeks on a low fat diet indicate (1) that this species, in common with other laboratory animals, will thrive on a diet low in fat, and (2) that it is not possible to lower the level of the blood or tissue lipids by removing fat and cholesterol from the diet.

It is generally believed that the liver and the fat depots are the sites of synthesis of neutral fat and phospholipid from carbohydrate and protein residues in the diet.[22] Certainly it has been shown that cholesterol can be synthesized in the animal body from acetate residues derived from any source, and that the site of this synthesis is probably in the liver.[23] We also know that the synthesis of

fat from carbohydrate is a continuous process even when only small amounts of carbohydrate are fed.[24] The reserve ability of this conversion mechanism may be very great, as we have been able to demonstrate by implanting stilboestrol pellets into chickens on a low fat diet.[25] In such animals we were able to obtain massive lipemia and hypercholesterolemia and the development of atherosclerosis.

Our data on fecal lipid excretion indicate two things: (a) a remarkable constancy of excretion over a given period; (b) this constancy is independent of diet, at least for the conditions of this experiment. Chickens on a low fat diet for over sixty weeks continue to excrete the same amount of fecal lipid as do the control birds on regular mash. These findings are in full accord with previous reports.[26] They again confirm the fact that fecal lipids are not predominantly dietary fats which have escaped absorption, but rather are secretions of the intestinal mucosa.

There is no doubt that fat restriction will lower the blood cholesterol and lipids in patients with essential xanthomatosis of the hypercholesterolemic variety.[29] The blood lipids of normal persons, however, are strongly resistant to change by fat restriction and/or fat overfeeding.[30] As an inference from the animal experiments, it would seem that the evidence at present does not warrant wholesale restriction of lipids in attempt to prevent the onset of arteriosclerosis. There is suggestive evidence, however, that fat restriction may be a judicious measure in patients with hypercholesterolemia even of a moderate degree, and possibly in patients with a bad family history of coronary or cerebral arteriosclerosis. Certainly any wider application of fat restriction must await more experimental justification.

SUMMARY

1. White leghorn cockerels, 6 to 10 weeks of age, were divided into two groups. Group 1 consisted of sixteen chickens which received in unlimited quantities a diet of chick starter mash and water. Group 2 consisted of fourteen chickens which received the same chick starter mash from which the fat and cholesterol had been largely removed by alcohol-ether extraction. This diet was made isocaloric by the addition of sucrose, and the vitamins removed in the extraction process were replaced. Feeding was continued for sixty-three weeks.

2. Gross atherosclerosis was seen in 35 per cent of the chickens on the low fat diet and in 63 per cent of the chickens on the control diet. The lesions appeared earlier and were more severe in the control group. The incidence of microscopically visible lesions was equal in both groups. There was no essential difference in the structure of the lesions.

3. The low fat group showed blood cholesterol levels which were consistently higher than those of the control group throughout the course of the experiment. Lipid analysis of the blood performed at the conclusion of the experiment revealed that all the lipid fractions of the blood were slightly higher in the low fat group than in the control group.

We are greatly indebted to the technical team whose efforts were essential for the proper execution of this study, and especially to Mrs. L. Havel and Miss C. Bolene, both Deborah V. Dauber Research Assistants, and to Miss Marilyn Dudley and Mrs. Eva Levinson, chemical technicians.

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ANTICOAGULATION THERAPY WITH HEPARIN/PITKIN MENSTRUUM IN THE MANAGEMENT OF CORONARY ARTERY THROMBOSIS AND ITS COMPLICATIONS

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ANTICOAGULATION therapy with heparin/Pitkin menstruum in the management of thromboembolic disease has been the subject of intensive study and prolonged trial.[1-9] Our aggregate series, totalling more than 450 patients with thrombotic disorders, received as the primary therapeutic measure several thousand subcutaneous deposits of heparin/Pitkin menstruum. The basic information gleaned from the comprehensive experimental study and clinical experience with this anticoagulation preparation in venous thromboembolism was applied in the treatment of patients with various types of arterial thrombotic lesions, including coronary artery occlusion. The response to the treatment program in a clinically and electrocardiographically authentic series of patients with acute coronary artery thrombosis was sufficiently gratifying to justify this preliminary communication.

CLINICAL MATERIAL

The twenty patients with coronary artery thrombosis comprising this series were all acutely, and many gravely, ill. This group of patients, the majority of whom had serious complications, were well suited for assessing the effects of anticoagulation therapy. The clinical features and electrocardiographic findings in all these patients were classical (Table I).

Ten (50 per cent) of the patients, five of whom had previous coronary artery closures, were referred three to seventy-two hours after onset during the early phases of the disease when optimum results from the treatment program might be expected. The ages of these patients, eight men and two women, varied from 35 to 64 years, the average age being 44 years. Three of this group developed anterior wall infarctions and seven had posterior wall lesions; five of the ten patients had thromboembolic complications.

The remaining ten patients (50 per cent), four of whom had had previous coronary attacks, were admitted for treatment six to fifty-six days after onset of the acute coronary occlusion. These patients, seven men and three women, were in a more advanced age group; their ages ranged from 47 to 76 years, the

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Table I. ...enstruum Therapy in Twenty Patients With Acute Coronary Artery Thrombosis

Case No.	Age	Sex	Significant Past History	Electrocardiographic Findings	Complications	Duration of Symptoms Before Heparinization	Heparin/Pitkin Menstruum Therapy: No. Days	Heparin/Pitkin Menstruum Therapy: No. Deposits	Heparin/Pitkin Menstruum Therapy: Total Heparin (Mg.)	Remarks
1 J. B.	45	F	None	Posterior wall infarction	Postoperative thrombophlebitis	3 hours	8	4	1,200	Classical symptoms coronary thrombosis 18 days after hysterectomy; uneventful recovery
2 W. P.	41	M	None	Anterior wall infarction with possible posterior wall involvement	Acute psychosis	4 hours	19	7	2,800	Ambulatory on 20th day; no post-therapy heparinization; venous thromboembolic disease 2 months after discharge
3 L. Z.	64	M	Hypertensive cardiovascular disease; coronary artery thrombosis	Posterolateral wall infarction		4 hours	18	9	3,350	Uneventful recovery
4 M. G.	35	M	None	Anterior wall infarction		9 hours	26	9	2,350	Unusually extensive coronary occlusion
5 A. G.	52	M	None	Posterolateral wall infarction		12 hours	13	6	2,150	Delayed electrocardiographic manifestations
6 L. N.	60	F	Hypertensive cardiovascular disease; effort syndrome; diabetes mellitus	Acute posterior wall infarction	Thrombophlebitis left lower extremity	24 hours	30	9	1,900	Good recovery from initial acute and subsequent fresh posterior wall infarction; heparin hyperreactor
7 B. F.	60	M	Coronary artery thrombosis; effort syndrome	Anterior wall infarction		24 hours	19	8	2,950	Uneventful recovery
8 H. B.	59	M	Atherosclerotic cardiovascular disease; coronary artery thrombosis	Posterior wall infarction superimposed on old myocardial changes	Recurrent thrombophlebitis; repeated embolizations	48 hours	18	8	2,600	Patient is a thrombophiliac; repeated pulmonary embolizations despite vein ligation and Dicumarol; satisfactory recovery with heparin
9 J. M.	42	M	Hypertensive cardiovascular disease; coronary artery thrombosis	Posterior wall infarction	Repeated pulmonary embolization	72 hours	26	10	3,150	Embolizations promptly arrested by therapy
10 M. R. B.	43	M	Coronary artery thrombosis (two attacks)	Posterior wall infarction superimposed on left ventricular strain	Pulmonary embolization; pleural effusion	72 hours	32	9	1,900	Patient is a thrombophiliac; three distinct episodes of venous thromboembolism despite vein ligation; heparin hyperreactor

11	M. O.	76	M	Hypertensive cardiovascular disease; coronary artery occlusion	Posterior wall infarction	Pulmonary infarction; pulmonary edema	6 days	40	9	2,450	Was in moribund state when treatment was inaugurated; satisfactory recovery
12	S. L.	47	M	Atherosclerotic cardiovascular disease; coronary artery occlusion	Posterior wall infarction	Venous thromboembolic disease; pulmonary embolization	6 days	25	9	3,200	Made spectacular recovery despite thrombophlebitis and pulmonary embolization which complicated second attack of coronary thrombosis
13	P. B.	52	F	Hypertensive cardiovascular disease; coronary artery thrombosis (two attacks); effort syndrome	Acute posterior wall infarction, left ventricular strain	Cerebral embolus from mural thrombus; hemiplegia; venous thromboembolic disease, pulmonary embolization	7 days	35	11	3,200	Excellent recovery from hemiplegia to such an extent that patient became ambulatory and speech returned practically to normal; patient is a thrombophiliac
14	J. G.	64	M	Atherosclerotic cardiovascular disease; coronary artery disease	Posterior wall infarction	Pulmonary embolization	7 days	24	8	2,500	Satisfactory recovery
15	C. H. H.	61	M	None	Anterior wall infarction; auricular fibrillation	Cerebral embolization, pulmonary edema; thrombophlebitis left lower extremity, pulmonary embolization	11 days	5	3	1,200	Therapy was started after patient was in coma and virtually moribund for 4 days
16	B. T.	59	M	Hypertensive cardiovascular disease	Anterior wall infarction, auricular fibrillation, auricular flutter	Venous thromboembolic disease, pulmonary embolization	14 days	24	9	2,850	Anticoagulation therapy begun after onset of bilateral phlebothrombosis and pulmonary embolization; uneventful recovery
17	U. R.	59	M	Coronary artery thrombosis	Posterior wall infarction		14 days	12	4	1,500	Uneventful recovery
18	M. H.	59	M	None	Anteroapical infarction	Cerebral artery embolization from mural thrombus	32 days	14	6	2,200	No further episodes of embolization once heparinization was inaugurated
19	V. M.	50	F	Coronary artery disease	Anterior wall infarction with some extracardiac changes	Splenic infarct; possible venous thromboembolic disease	42 days	24	10	2,900	Transitory nausea following injections; uneventful recovery
20	E. S.	58	F	Hypertensive cardiovascular disease; effort syndrome; diabetes mellitus	Posterior wall infarction	Venous thromboembolic disease; repeated pulmonary embolization	56 days	21	7	2,250	Repeated pulmonary embolization despite Dicumarol; prompt termination of thromboembolic episodes with heparin therapy

average being 58 years. Four of this group sustained anterior wall infarctions and six had posterior wall lesions. The high incidence (90 per cent) of thromboembolic complications, which was primarily responsible for instituting anticoagulation therapy, may be ascribable in part to the fact that these ten patients were in a generally older age group.

The gravity and prognostic import of the clinical manifestations in this series is but superficially portrayed in the tabulation of data. The appearance of clinically detectable, complicating thromboembolic episodes in fourteen of the twenty patients (70 per cent), as against a reported expectancy of 13.9 per cent,[10] is a reflection of the degree of myocardial involvement and resultant circulatory embarrassment.

TREATMENT PROGRAM

A detailed description of the heparin/Pitkin menstruum preparation, including the rationale, indications, contraindications, and the various formulas which are now available,* has been presented in previous publications.[1-5, 9,11] As pointed out in these reports, it is essential to use the preparations without vasoconstrictor drugs in the management of patients with intra-arterial clotting, particularly when dealing with coronary artery thrombosis. In these patients it is important to achieve prompt and maximum anticoagulation responses. Therefore, the initial dose of heparin in the Pitkin menstruum should be at least 400 mg., administered subcutaneously in the usual manner. About 90 per cent of subjects are normal reactors; the remaining 10 per cent are either hyporeactors or hyperreactors and require greater or lesser dosages, respectively. All coagulation time determinations are estimated by a modified Lee-White-Howell method.[12] For effective heparinization the blood coagulation time should be not less than three times the control value, that is, 30 to 45 minutes, as contrasted with a control coagulogram of 9 to 15 minutes. Prolongation of coagulation time after each individual deposit appears within one to two hours and endures for forty-eight hours or longer as a result of the retarding influence of the Pitkin menstruum (Fig. 1). It is comforting to know that injection of larger doses to insure satistory heparinization does not invite the hazard of excessive doses of Dicumarol. the patient with an intact cardiovascular apparatus there is little or no risk hemorrhage, even following excessive amounts of heparin sufficient to elevate e coagulation time considerably beyond the requisite level.

After the pattern of response has been ascertained, the subsequent injections can be made more or less routine. Repetitive doses of 400 mg. are generally given every other day during the acute thrombotic phase in order to prevent propagation and to promote resolution of the thrombus. This schedule should be maintained for three to four implants to achieve a continuous and adequate heparin response. Thereafter, if justified by the anticoagulation effects, the individual dose may be given at longer intervals and the amount of the drug per dose reduced to 300 mg. or even 200 mg., as dictated by the specific case. Occasionally, in the initial phases, deposits may have to be given on successive days in order to obtain optimum and sustained heparinization. As in venous throm-

*Prepared and distributed by William R. Warner & Co., Inc., New York, N. Y.

boembolic disease, the span of treatment must be continued at least until the patient is permitted out of bed. Occasionally patients who are on heparin therapy may, following abrupt withdrawal of the drug, develop a diphasic phenomenon wherein the blood becomes hypercoagulable. This phenomenon is obviated by a gradual decrease of the heparin/Pitkin menstruum therapy.

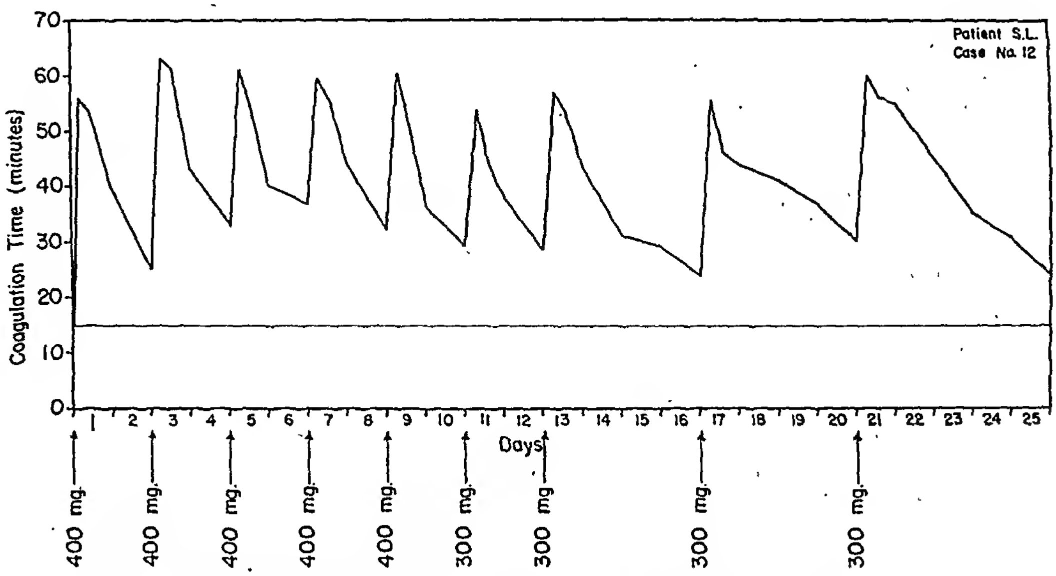

Fig. 1.—Coagulogram of heparin/Pitkin menstruum treatment program in a normal reactor.

The local pain, swelling, and tenderness of the earlier experimental, highly acid preparation was due to the precipitate which was found to be a combination of heparin and eucupine. The pain factor induced by the acidity and precipitate of the preparation was at times excessive but could be controlled by adequate sedation. This objection to the original preparation, the pain factor which was so disturbing to the patient, has now been controlled by careful buffering so that the pH of the gel is more acceptable physiologically and the tendency to precipitation noted in the original ampules has been overcome. Other side effects of the heparin/Pitkin menstruum preparation are trivial.[1-5, 7,9] On rare occasions some oozing will occur from the needle puncture. In the several thousand deposits that have been made there was but one instance of hematoma of sufficient proportion to justify interruption of heparinization; this patient with post-partum thrombophlebitis made an uneventful recovery.

Although we have not elicited any direct thromboplastic effect of digitalis, the drug has been reported to inhibit the anticoagulant action of heparin.[13,14] If possible, therefore, the use of digitalis is to be avoided during the period of heparinization. If suspension of heparin activity is desired, small transfusions of whole blood or relatively fresh bank blood will inactivate any circulating heparin. An ice bag to the site of deposit, or a tourniquet above it, will suspend or slow up the absorption of the drug. In our experience the use of protamine for immediate interruption of heparinization has not been necessary.

Adjuvant drug therapy is employed uniformly for sedation and to overcome vasospasm. For these purposes morphine sulfate, in adequate amounts, and Papaverine, in dosages of one and one-half to three grains intravenously or intramuscularly every four hours, remain the drugs of choice. These should be administered as promptly as possible after the onset of the characteristic pain. Ideally, the conjoint therapeutic attack at the very outset should be intravenous morphine, intramuscular Papaverine, and subcutaneous heparin in the Pitkin menstruum.

RESULTS

The results in this exploratory study of twenty consecutive, unselected patients with acute coronary thrombosis are noted in Table I. Of the twenty patients, there was but one fatality (5 per cent); this patient (Case 15) had been desperately ill for eleven days and was moribund before anticoagulation therapy was inaugurated. This treatment failure occurred among the fourteen patients who exhibited thromboembolic complications. A brief review of Case 15 follows:

CASE 15.—C. H. H., a 61-year-old white man, a business executive, was admitted to the Lawrence Hospital, Bronxville, N. Y., under the care of Dr. H. E. McGarvey. The patient had a past history of "nervous stomach" since childhood. One day before admission he developed flatulence with increasing, constant, dull epigastric pain, dyspnea, and shock. His blood pressure was 100/72. On the midnight prior to admission the acute abdominal distress was of such severity that a surgical condition was suspected. A leucocytosis of 15,000 with 88 per cent polymorphonuclear leucocytes apparently pointed in the same direction. Two days later he developed a consolidation at the base of the right lung with a friction rub over the apical area of the heart; the heart sounds became less distinct and the clinical picture justified a diagnosis of coronary artery thrombosis. The following day the heart sounds were much poorer in quality. He developed cardiac embarrassment and mild shock, and his condition rapidly became critical. Successive electrocardiograms disclosed findings characteristic of an anterior myocardial infarction and auricular fibrillation. Seven days after onset the patient developed pulmonary edema and lapsed into a coma which was ascribed to extensive cerebral embolization from an intracardiac mural thrombus. On the eleventh day of his illness he exhibited right thrombophlebitis with massive pulmonary embolization. The congestive failure was advanced; he was comatose and practically moribund. Heparin/Pitkin menstruum was instituted at this juncture. Despite adequate anticoagulation responses, the patient rapidly deteriorated; he never regained consciousness and succumbed on the sixteenth day of his illness. He had, in all, five days of therapy with a total of 1,200 mg. of heparin in the Pitkin menstruum deposited in three injections

Comment.—This patient with anterior wall infarction and auricular fibrillation had cerebral embolization from an intracardiac mural thrombus and massive pulmonary embolization from peripheral vein thrombosis. When treatment was inaugurated the patient was in coma and desperately ill. Notwithstanding the gravity of the condition, anticoagulation therapy was started and proved unavailing after a five-day span of therapy.

All the remaining nineteen patients recovered despite previous coronary attacks and complicating thromboembolic episodes in a large percentage of the group. There are included the ten patients who were treated within three to seventy-two hours after onset of the acute coronary occlusion and the four patients whose prognosis was just as ominous as that in Case 15. Brief reviews of some illustrative cases in this group follow:

CASE 4.—M. G., a 35-year-old white physician, was referred for treatment* nine hours after the onset of his symptoms. This patient, who had never had any previous evidence of cardiovascular disease, was admitted to City Hospital, New York City, on May 2, 1947, with a history of sudden, excruciating, substernal, nonradiating pain of three hours' duration. On examination he was found to be very apprehensive and restless. He was in shock and slight cyanosis of the lips was present. The heart sounds were of only fair quality. The systolic blood pressure was 110, as compared with his normal of 130 millimeters of mercury. Temperature on admission was 98° F.; this rose to 103°F. on the following day and remained elevated for six days. The electrocardiogram on admission (Fig. 2) confirmed the diagnosis of acute myocardial infarction of the anterior wall type. Nine hours after the onset, anticoagulation therapy was instituted with 300 mg. of heparin in the Pitkin menstruum. The following day a similar dose was given because of the inadequate anticoagulation response. In all, the patient was given a total of 2,350 mg. of heparin/Pitkin menstruum deposited in nine injections over a period of twenty-six days. Periodic electrocardiograms taken during the course of the treatment disclosed progressive healing (Fig. 2), so much so that the patient was allowed out of bed after four weeks and was finally discharged after five and one-half weeks of hospitalization. There were no thromboembolic episodes or other untoward complications and there were no clinically evident residua.

Comment.—This patient was in critical condition when first seen following the unheralded attack of acute, severe myocardial infarction. Heparinization was initiated nine hours after onset. As a result of the prompt institution of anticoagulation therapy, the electrocardiograms, which on admission confirmed the presence of an acute anterior wall infarction, revealed progressive healing of the infarcted area so that the patient was able to get out of bed after twenty-six days of treatment and discharged from the hospital five and one-half weeks after admission. There was concurrent improvement in the clinical picture and there were no thromboembolic or other complications.

CASE 6.—L. N., a 60-year-old white housewife, was referred for treatment twenty-four hours after recurrent myocardial infarction. This patient, with a background of hypertensive, atherosclerotic cardiovascular disease and diabetes mellitus, had for six years typical angina of effort from which she obtained relief with nitroglycerine. Six weeks prior to her admission to the Beth Moses Hospital of Brooklyn, on March 15, 1947, the patient had a sudden attack of precordial pain with concomitant shock. A diagnosis of acute posterior wall infarction was made which was substantiated by electrocardiographic tracings. While getting out of bed, after six weeks of bed rest, the patient sustained an acute thrombophlebitis of the left leg with a rise in temperature. Twenty-four hours before admission there was a recurrence of severe precordial pain. On examination she exhibited shock, marked pallor, and distant heart sounds of very poor quality. There was also pain, tenderness, heat, and redness of the left calf. A diagnosis of coronary thrombosis and thrombophlebitis of the left lower extremity was made. A pretreatment electrocardiogram (Fig. 3) was interpreted as indicating an acute, posterior myocardial infarction with sinus tachycardia. Follow-up electrocardiograms taken during the course of treatment with heparin/Pitkin menstruum, which was begun promptly after admission, revealed progressive improvement (Fig. 3). The patient was a hyporeactor and required a total of 1,900 mg., given in nine injections over a period of thirty days. During this span of treatment the patient had no subjective complaints, the heart sounds improved, blood pressure gradually attained a higher level, and the thrombophlebitis of the left leg subsided completely.

Comment.—This patient, with thrombophilia and a background of hypertensive, atherosclerotic cardiovascular disease and diabetes mellitus, originally sustained an acute coronary closure with myocardial infarction which was treated in the usual manner with six weeks of bed rest. As a result of the venostasis, she developed an acute thrombophlebitis of the left lower extremity and in addition suffered an extension of the coronary artery thrombosis. With heparin/Pitkin menstruum therapy there was a reversion of the electrocardiogram toward normal within seven

*We wish to thank Dr. E. S. Bernecker, Commissioner, Department of Hospitals, New York City, for his interest and cooperation in referring clinical material for this study.

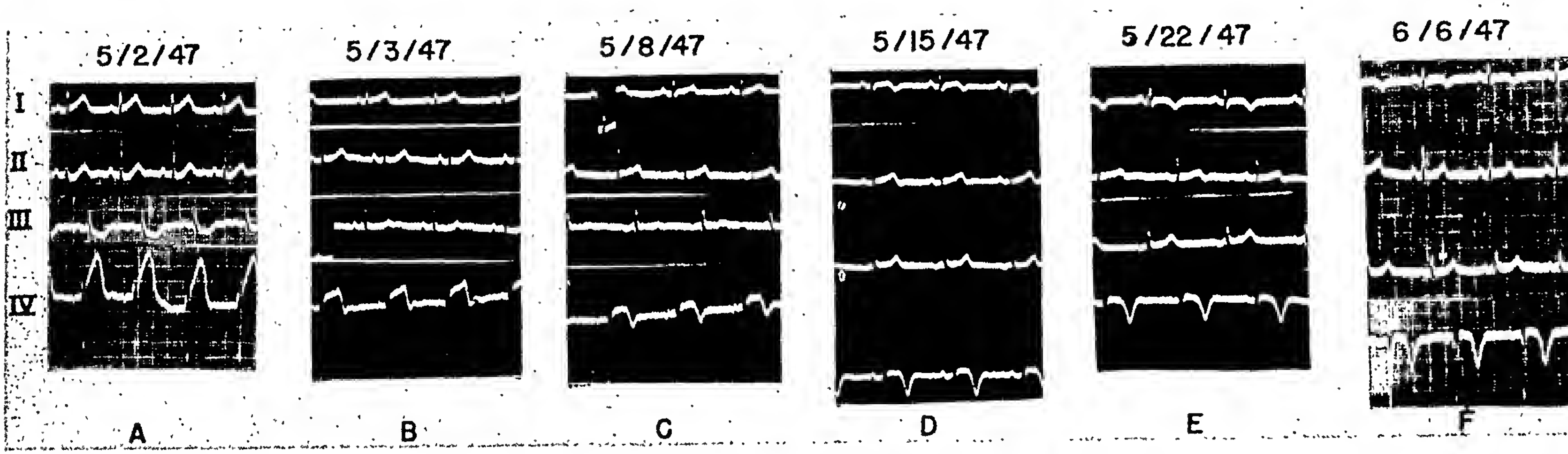

Fig. 2.—Case 4. *A*, Acute coronary thrombosis with myocardial infarction of anterior wall; pretreatment. *B*, T_3 is less depressed and T_4 is nearer isoelectric level. *C*, Tracing after seven days of therapy. *D*, Healing anterior myocardial infarction thirteen days after onset. *E*, Definite healing of infarct. *F*, Healed coronary thrombosis with infarction thirty-four days after onset; treated with a total of 2,350 mg. heparin/Pitkin menstruum over a period of twenty-six days.

days. She is presently, some sixteen months after the acute attack, free of all subjective pain and there has been almost complete amelioration of the effort syndrome. As a result of this improvement she has been able to resume partial duties as a housewife.

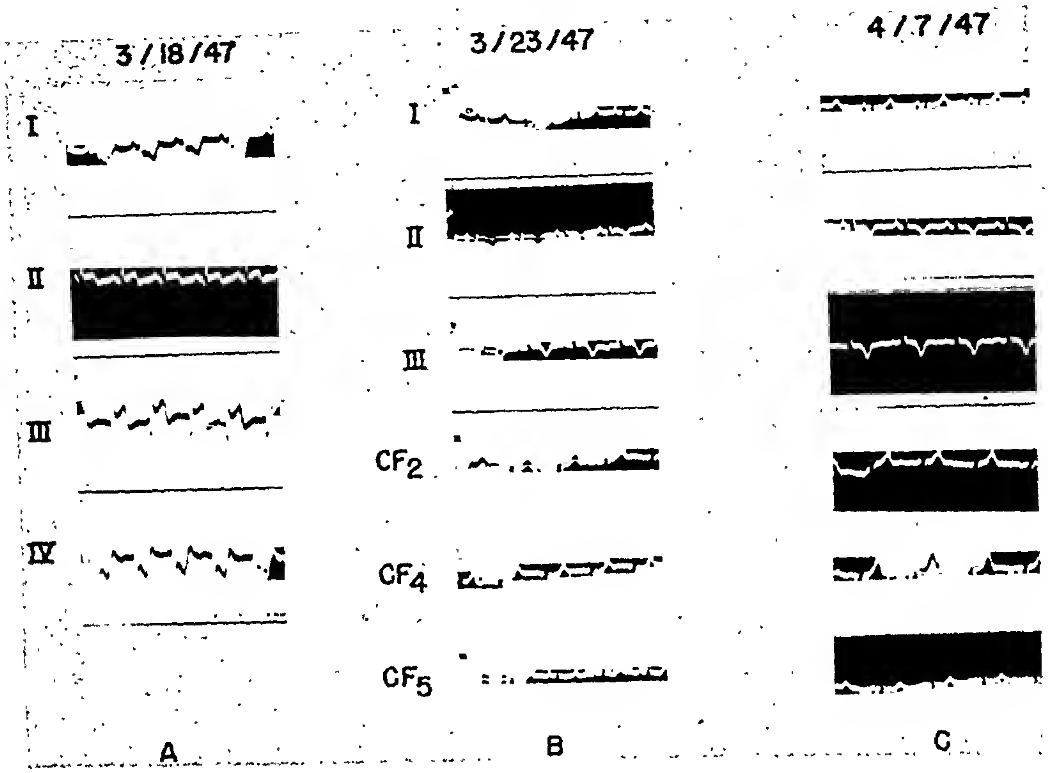

Fig. 3.—Case 6. *A*, Pretreatment extension of acute coronary thrombosis (posterior wall infarction) in hypertensive, diabetic woman, following six weeks of bed rest. *B* and *C*, Subsequent tracings five and twenty-two days following start of heparin/Pitkin menstruum therapy, showing residual posterior wall myocardial lesion.

Case 8.—H. B., a 59-year-old white man, a plumbing contractor, was first seen six months after the original myocardial infarction. This attack, which was substantiated electrocardiographically, was treated at home with bed rest and the usual medication. After six weeks in bed, he developed thrombophlebitis of the left lower extremity which was followed by another severe attack of precordial pain. He was treated at home with Dicumarol and penicillin, despite which he had recurrent pulmonary embolizations. The patient was thereupon hospitalized for bilateral femoral vein ligation following which he continued to run a persistent low-grade temperature. Adequate Dicumarol therapy and large doses of penicillin were administered throughout the entire hospital stay. On the day after discharge from the hospital he had recurrence of the thrombophlebitis involving both lower extremities with complicating massive pulmonary embolization. The patient was seen at home on Aug. 9, 1946, at which time he was given a deposit of 350 mg. of heparin/Pitkin menstruum and referred immediately to the Jewish Hospital. An admission electrocardiogram was indicative of a recent posterior wall infarction superimposed on old myocardial damage. He was given a total of 2,600 mg. of heparin divided into eight deposits over a period of eighteen days, during which time he made satisfactory progress, clinically and electrocardiographically. There were no further thromboembolic episodes and the patient was allowed out of bed after nineteen days of bed rest. The patient has been given modest periodic prophylactic deposits of heparin for the past year, during which time he has felt perfectly well and has been able to resume his occupation as a plumbing contractor.

Comment.—This patient is an exquisite thrombophiliac who suffered two attacks of acute coronary thrombosis and recurrent thrombophlebitis with repeated pulmonary embolizations. Dicumarol and femoral vein ligation failed to control the thromboembolic complications. Immediately after the initial deposit of heparin/Pitkin menstruum, extension of the coronary artery thrombosis was obviated and the thromboembolic complications were controlled. The response to the curative heparin/Pitkin menstruum therapy was most gratifying and throughout the prophylactic program there were no further thrombotic incidents.

CASE 10.—M. R. B., a 43-year-old, obese white physician, was first admitted to the Jewish Hospital of Brooklyn on Nov. 25, 1944. Five months prior to this admission he had a thrombophlebitis of the right leg for which the right femoral vein was ligated. Two weeks before this admission he had an episode of hemoptysis with elevation of temperature which was diagnosed as pulmonary infarction. He was hospitalized when the chest pain, cough, and fever continued and he developed signs of pleural effusion in the left pleural cavity. During this hospital stay he developed migratory thrombophlebitis of the left lower extremity with a rise in temperature. With conservative therapy all symptoms and signs abated and he was permitted to go home. Three days before the present admission, April 4, 1947, the patient was seized with a most agonizing attack of substernal pain of several hours' duration. This was obviously due to an acute myocardial infarction which an electrocardiogram showed to be of the posterior wall variety. Two days later he developed temperature and experienced pain at the base of the left lung. This pain persisted to the day of admission, and in view of the corroborative physical findings, was attributed to pulmonary infarction. A short pleuropericardial friction rub was heard at the left border of the heart. The admission electrocardiogram substantiated the diagnosis of acute posterior wall infarction. Anticoagulation therapy was instituted at once and he received a total of 1,900 mg. of heparin in the Pitkin menstruum distributed over nine deposits given over a period of thirty-two days. Although the patient was an extreme thrombophiliac, he was also a hyperreactor and obtained excellent heparin responses from relatively small doses (100 to 200 milligrams). The heart sounds, which originally were of only fair quality, improved. There were no further thromboembolic episodes and the patient was permitted out of bed less than four weeks after onset. He was placed on a prophylactic heparin program with satisfactory results to date.

Comment.—This obese thrombophiliac, who had recurrent attacks of thromboembolic disease despite vein ligation, suffered a third attack of acute coronary artery thrombosis. He was a heparin hyperreactor and maintained satisfactory anticoagulation effects with modest doses of heparin/Pitkin menstruum. The response to the treatment program was noteworthy, so much so that he has now resumed the practice of ophthalmology.

CASE 12.—S. L., a 47-year-old white man, a designer by occupation, was admitted to the Jewish Hospital of Brooklyn on June 12, 1947. This patient with atherosclerotic cardiovascular disease and parkinsonism had an acute attack of coronary artery thrombosis about one year prior to his present admission for which he was treated with the customary six weeks of bed rest. Ten days before admission he sustained trauma to the left tibia. Several days later he had pain in the left popliteal fossa which lasted twenty-four hours. Six days prior to admission he developed pain in the left chest which was sudden in onset and associated with dyspnea and shock. A diagnosis of coronary thrombosis with myocardial infarction was made and the patient put at bed rest. Two days later he developed a second episode of left axillary chest pain with severe dyspnea and was told that he had developed pneumonia which, however, did not respond to penicillin therapy. On the day of admission, the patient was in partial collapse, dyspneic, and cyanotic. The heart sounds were distant and there was a diastolic gallop rhythm with an impure first sound; congestive râles were audible over the posterior aspect of the lungs. The blood pressure was 106/60, as contrasted with his usual pressure of 170/90. The diagnosis was thromboembolic disease complicating acute coronary thrombosis with myocardial infarction. The presence of a posterior wall lesion was borne out by electrocardiograms taken on, and subsequent to, admission. The prognosis was considered to be extremely grave and, because of the advanced condition, prompt recourse was had to anticoagulation therapy as the only possible remedial measure. Heparin/Pitkin menstruum therapy was inaugurated immediately and continued for a period of twenty-five

days, a total of 3,200 mg. being administered in nine deposits. His response was spectacular and he was allowed out of bed on the nineteenth hospital day. He became ambulatory without much difficulty and was discharged from the hospital on the twenty-sixth day.

Comment.—This patient with atherosclerotic cardiovascular disease and parkinsonism was diagnosed originally as having an acute coronary artery thrombosis with a supposed complicating bronchopneumonia. The clinical picture on admission suggested pulmonary embolization complicating the coronary thrombosis and explained the ineffectiveness of penicillin therapy. The patient was in a deplorable condition. Heparinization was immediately started and continued for twenty-one days without the simultaneous administration of penicillin. This patient illustrates the effectiveness of the treatment in curtailing the period of bed rest, only nineteen days being required, as against a customary minimum of six weeks in a case of this gravity.

CASE 13.—P. B., a 52-year-old white housewife, was known to have hypertension for many years with a systolic blood pressure of 240 millimeters of mercury. Six years prior to her admission to the Jewish Hospital of Brooklyn, Nov. 19, 1946, on the service of Dr. E. L. Shlevin, she began to complain of occasional precordial oppressive pain with radiation to the left arm. Soon afterward she was confined to bed for approximately sixteen weeks because of acute myocardial infarction, during which time she sustained a bilateral thrombophlebitis. Three years afterward she had a second coronary artery occlusion. Four days before hospitalization she had typical signs of acute coronary closure with shock, precordial pain, apprehension, and precipitate drop in blood pressure. The clinical diagnosis was confirmed by electrocardiographic evidence which indicated an acute posterior wall infarction (Fig. 4). Her systolic blood pressure, which was usually around 240, was now 120 mm. Hg, and there was slight elevation of temperature and leucocytosis. Twenty-four hours after admission she exhibited a right hemiplegia attributed to embolization from an intracardiac mural thrombus. The patient became confused and uncooperative, and the prognosis appeared extremely grave. The next day she had severe precordial pain and developed a protodiastolic gallop rhythm and it was felt that she had sustained a pulmonary embolus. Twenty-four hours later she had pain in her right leg and presented the clinical features of an acute thrombophlebitis. Within a period of seven days, the patient had acute coronary artery thrombosis, cerebral embolization, and right thrombophlebitis. Her condition was grave and recourse was had to anticoagulation therapy. Twenty-four hours after the first deposit of 450 mg. of heparin in the Pitkin menstruum the patient had a partial return of speech. It will be noted that the initial dose was 450 mg. instead of the usual 350 to 400 mg. because of the condition of the patient and the extent of thrombotic involvement. She was treated intensively for twenty-three days with a total of 2,650 mg. of heparin divided into eight subcutaneous deposits, and her condition improved in a most satisfactory manner. Thereafter, and until discharge, she was placed on periodic, reduced (150 mg.) maintenance dosages of heparin for prophylaxis. She began to regain almost complete use of her extremities, recovered her speech, became less confused and more cooperative, and eventually was permitted out of bed on the twenty-ninth day of heparin therapy. In all, the patient was given eleven deposits of heparin/Pitkin menstruum for a total of 3,200 mg. over a period of thirty-five days, after which she was able to leave the hospital. She could walk unaided, and except for residual mild facial paralysis, her condition was most satisfactory.

Comment.—Within seven days this patient exhibited coronary artery thrombosis with myocardial infarction, cerebral artery embolization from an intracardiac mural thrombus, and venous thromboembolic disease with pulmonary embolization. She is an extreme example of thrombophilia with a background of hypertensive atherosclerotic cardiovascular disease. She was almost moribund prior to treatment and progressed favorably from the very outset of therapy. The extension of the coronary artery thrombosis was averted, all complicating thromboembolic episodes were prevented, and restoration of the vascular stream in the occluded vessels was promoted. The treatment program was intensified because of the widespread nature of the process. Attention is called to the fact that the major response was evident within the twenty-three days of intensive therapy.

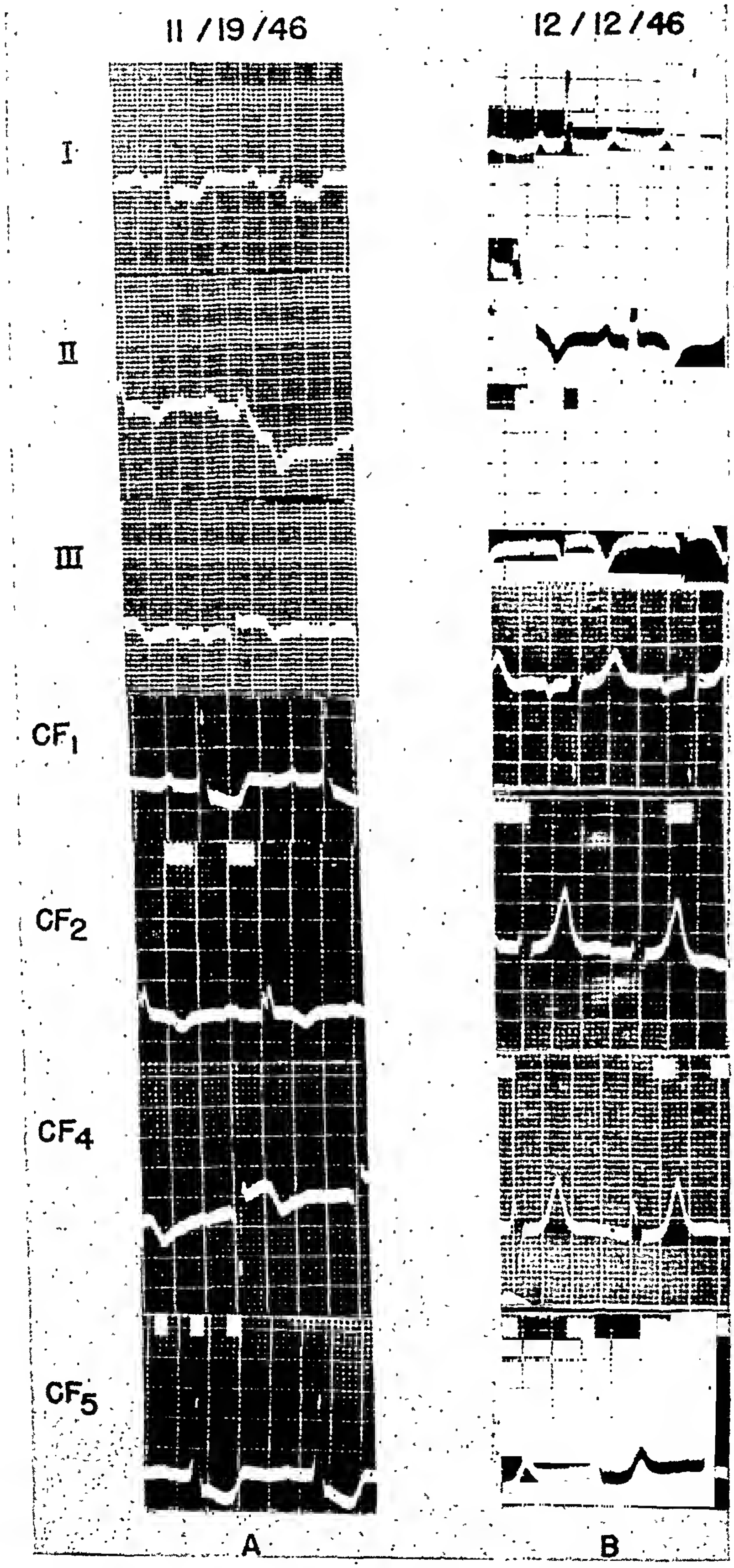

Fig. 4.—Case 13. *A*, Acute posterior wall infarction with some anterior wall involvement; followed by cerebral embolus with hemiplegia, pulmonary embolus, and thrombophlebitis. Patient in coma and moribund at start of therapy. *B*, Electrocardiogram twenty-four days later showing return toward normal. Satisfactory recovery after twenty-three days of intensive heparinization.

CASE 16.—B. T., a 59-year-old white man, was a known hypertensive for the previous eight to nine years but had always been asymptomatic except for occasional headaches. Forty hours prior to his admission, the patient was awakened at night with a burning substernal pain associated with epigastric distress. The pain radiated through to the back of the chest and left shoulder. He walked around that day and consulted his local physician that night, at which time an electrocardiogram revealed auricular flutter. He was admitted to the Jewish Hospital on July 16, 1946,

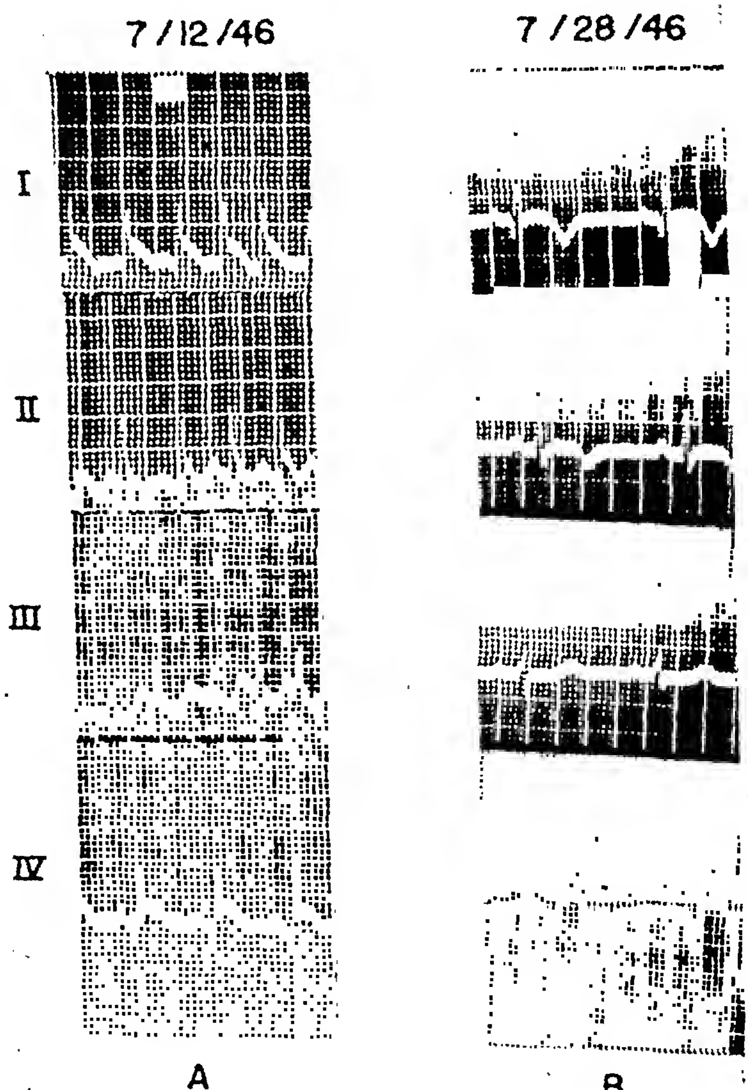

Fig. 5.—Case 16. *A*, Auricular flutter eighteen days before institution of therapy. *B*, Acute anterior wall infarction three days before institution of therapy. In the interim patient sustained thrombophlebitis and pulmonary embolization. *No further thromboembolic episodes after start of heparinization.*

service of Dr. E. L. Shlevin, with a temperature of 100.5°F., a pulse rate of 90, and respirations of 24 per minute. The systolic blood pressure, ordinarily over 200, was now 160 millimeters of mercury. He was in severe pain and distress with cyanosis of the lips and nails. He had a trigeminal rhythm for which quinidine therapy was prescribed. The electrocardiogram (Fig. 5) on admission again disclosed auricular flutter. The next day he had severe precordial pain with a heart rate of 160

per minute. He was given oxygen, morphine, and atropine with some relief. The cardiac irregularity continued the next day and the dosage of quinidine was increased. Twenty-four hours later he had bilateral calf tenderness which disappeared spontaneously. Two weeks after admission he was awakened with sudden pain in the right anterior chest which became excruciating on deep inspiration. It was fairly evident that the patient had sustained a pulmonary embolization. The next day anticoagulation therapy was begun with heparin/Pitkin menstruum. Two days later he still had marked chest pain over the right lower lobe on inspiration; a bedside roentgenogram of the chest was negative (it was impossible to obtain the oblique views necessary to properly visualize early pulmonary infarction). Eight days after the beginning of anticoagulation therapy his general condition was much improved; the temperature was normal, but he still had dullness over the right posterior lung base with a pleural friction rub. An interim electrocardiogram (Fig. 5, *B*) showed a recent anterior wall infarction with no evident quinidine effect. The patient continued to make satisfactory progress and eleven days after heparinization was started the entire chest was clear. Four days later he was allowed to sit in bed and several days afterward he was permitted out of bed, at which time he had no complaints. A total of 2,850 mg. of heparin/Pitkin menstruum was given in nine deposits over a period of twenty-four days.

Comment.—This patient had multiple thromboembolic complications associated with the original coronary thrombosis over a period of two weeks, during which time he was treated with the conventional methods of therapy. It was only after the institution of anticoagulation therapy with heparin/Pitkin menstruum that the thromboembolic episodes were arrested. He had no further clot propagation or embolizations.

DISCUSSION

Coronary artery thrombosis offers a very attractive field for anticoagulation therapy. Reports have already appeared which indicate that this form of therapy holds great promise.[15-19] A triphasic therapeutic attack is admittedly indicated in coronary artery thrombosis. The first and most important objective is to prevent central propagation of the thrombus from what, in many instances, is merely an occlusive involvement of a small twig of a coronary vessel. In this manner it is possible to limit the degree of myocardial infarction and resultant myocardial damage. All too often the propagation thrombus is the lethal factor. The second objective is the prevention of embolization from mural thrombi secondary to the myocardial infarction. The third phase of the therapy is levelled at the not infrequent complicating thrombosis of deep venous channels resulting from slowing of the vascular stream in the bedridden convalescent patient; the subsequent, at times ominous, pulmonary embolizations may be clinically confusing. For optimum effects the immediate administration of anticoagulation therapy is essential. One cannot advocate too strongly that the prompt inauguration of this therapy may be life saving and, of course, serves to minimize the ultimate damage.

In 1940 Best[20] suggested that the clinical cardiologist explore the possibilities of heparin in acute coronary thrombosis. Despite early encouraging results, this treatment approach was abandoned primarily because of the technical difficulty of administering heparin in its aqueous form, especially in cardiac cases. The anticoagulation treatment approach was revived by Nichol and Page,[16] Peters, Guythier, and Brambel,[17] Wright,[18] and Parker and Barker[19] when Dicumarol became available for clinical use.

Recourse to Dicumarol is understandable because it can be administered orally. The effectiveness of the drug, however, is tempered by the difficulty

in planning dosage schedules and, more important, because of its occasional dangerous complications.[21,22,23] There is considerable variability in the response to Dicumarol, this lack of uniformity of response being present even in the same individual. Fixed dosage schedules cannot be established; patients must be individualized. The action of Dicumarol is slow, twenty-four hours or longer being required before its therapeutic effectiveness is achieved. Because of this delay in action and the variability of the patient's response, the drug is not useful in the early, critical stages of coronary thrombosis. Patients receiving Dicumarol require daily prothrombin determinations. The use of Dicumarol should not be countenanced unless there are proper laboratory facilities for prothrombin determinations by acceptable techniques. The latter are time consuming and relatively expensive.

Unlike heparin, the presence of liver and/or kidney disease militates against the use of Dicumarol. This is a disadvantage in patients with coronary thrombosis who so often have generalized atherosclerotic cardiovascular disease with renal involvement. Dicumarol has been attended with irreversible hemorrhage and death.[24] Transfusions of fresh blood alone do not always arrest the hemorrhagic tendency occasioned by the drug. Massive dosages of vitamin K are required which may, occasionally, reinduce thrombosis.[25]

In summary, then, the delayed action, contraindications, potential hazards, the unpredictable treatment failures, and the requisite, complicated, but indispensable laboratory procedures militate against Dicumarol as the anticoagulant of choice in coronary artery thrombosis. Furthermore, although the technical difficulties and hazards of administering Dicumarol are recognized and have been surmounted to some extent, the drug is not an effective agent during the initial, critical phase of acute coronary artery thrombosis. In addition, the use of Dicumarol presents difficulties in the attempt to carry out a protracted, prophylactic anticoagulation program. The relative merits of heparin and Dicumarol are compared in Table II.

The properties of heparin which render it uniquely applicable in thromboembolic disease are that it prevents, with the aid of a plasma cofactor, the conversion of prothrombin to thrombin; it forms with serum albumin a strong antithrombin; and, finally, it prevents the formation of thromboplastin from platelets.[26] The properties of heparin predicate the fact that a clot, regardless of its site or stage, cannot propagate in the presence of heparin. However, what happens to the clot which is already present?

It has been possible to determine experimentally at what stage of clot formation heparin administration results in solution of the clot and what effects heparin has on the organizing clot.[3-11]

Briefly, studies on the effect of heparin on experimental thrombosis have yielded the following data:

1. Red cell clots which are not organized and contain a minute amount of fibrin (sludge stage) disappear completely under heparin therapy.

2. Heparin therapy maintains patent adjacent collaterals and tributaries which ordinarily would become involved in the thrombotic occlusive process. The compensatory collaterals often become as large as the originally occluded

vessel. This phenomenon has not been observed in control veins. It may be assumed, though not necessarily proved, that these processes also occur in obstructed lymphatics.

TABLE II. COMPARISON OF THE ADVANTAGES AND DISADVANTAGES OF HEPARIN/PITKIN MENSTRUUM AND DICUMAROL

	HEPARIN/PITKIN MENSTRUUM	DICUMAROL
Dosage	Initial dose 400 mg.; thereafter, 300 to 400 mg. as indicated.	No standard dosage; completely dependent upon daily prothrombin determinations
Control	Simple coagulogram at bedside	Daily precise prothrombin time determined in laboratory
Response	Prompt anticoagulant response within 1 to 2 hours; consistent and predictable; each injection effective for 48 hours or longer	Lag in effect for 24 hours or longer; unpredictable response necessitating individualization of dosage schedule
Administration	Subcutaneous; advantage only in moribund cases	Oral; advantage except in comatose patients
Contraindication	Active bleeding	Active bleeding, renal disease, hepatic disease
Clinical use	All venous and acute arterial thromboembolic disease	Lag effect of Dicumarol necessitates initial conjoint use of heparin in acute arterial lesions
Complications of overdosage	None with intact cardiovascular system	Hemorrhage
For interruption of therapy	1. Ice bag to site of heparin deposit 2. Small whole blood transfusion 3. Protamine, intravenously*	1. Vitamin K intravenously (may reinduce thrombosis) 2. One or more 250 to 500 c.c. whole fresh blood transfusions

*The use of protamine has never been required in the course of several thousand deposits of heparin/Pitkin menstruum.

For abrupt termination of progression of the initial thrombotic process, which is the most urgent objective, heparin is the anticoagulant of choice. Heparin in the Pitkin menstruum, because of its effectiveness, prompt action, and simplicity of administration, appears to be the preparation best suited for the treatment of acute coronary artery thrombosis.

While this series is much too small to permit detailed statistical analysis, a conservative review of mortality and morbidity data is enlightening in view of the almost uniform gravity of the twenty patients comprising the group.

A generally poor pretreatment prognosis was justified in this group for the following reasons:

1. Only three (15 per cent) of the twenty patients had an initial, uncomplicated attack of coronary artery thrombosis. While it is ordinarily hazardous to predict the outcome in this type of case, all three patients (Cases 2, 4, and 5) were relatively young; all had extensive myocardial infarction; and all were desperately ill. The clinical and electrocardiographic picture warranted an ominous

prognosis in all three patients. Recovery with minimum residue in all three may be attributed in part to the early administration of anticoagulation therapy, four, nine, and twelve hours, respectively, after onset of the attack.

2. Nine patients (45 per cent) had antecedent attacks of coronary artery thrombosis. These patients with a previously compromised coronary artery tree had an increasingly unfavorable outlook. This is especially true of the six patients who, in addition, had complicating thromboembolic episodes. The treatment program may well have been an important factor in the recovery of all nine of these patients.

3. A total of fourteen (70 per cent) patients had one or more complicating thromboembolic episodes. Four had arterial embolizations from mural intracardiac thrombi; three of these had, in addition, venous thromboembolic disease. Of the latter, Case 15 (our only treatment failure, first seen in a moribund state eleven days after the coronary occlusion) succumbed to the combination of anterior wall infarction, auricular fibrillation, cerebral embolization, pulmonary edema, thrombophlebitis, and massive pulmonary embolization. Case 13 with an almost identical clinical syndrome made a spectacular recovery despite multiple arterial and venous thromboembolic episodes over a period of seven days. Ten patients had pulmonary embolizations, at times multiple, mostly from peripheral vein thrombosis.

It is interesting to collate the mortality figures in cases of a comparable nature. The average mortality of uncomplicated acute coronary artery thrombosis varies from 20 to 30 per cent.[18] Of the twenty patients in our series, six were in this category and all recovered. This is suggestive, but inconclusive because of the limited number of patients. More significant is the estimated 60 to 70 per cent mortality for coronary artery thrombosis with complicating thromboembolic phenomena,[18] which compares with one treatment failure (7 per cent) in the fourteen patients comprising the group of complicated cases.

An analysis of the morbidity, clinical picture, and progress of both the uncomplicated and the complicated cases during and after the treatment program is revealing. In the absence of anticoagulation therapy, an unpredictable number of these desperately ill patients might conceivably have sustained increase in the area of myocardial infarction as a result of propagation of the thrombus in the occluded coronary artery, or secondary coronary occlusions with resultant multiple infarctions. Furthermore, there was every reason to believe that some of the uncomplicated cases would develop embolic phenomena from intracardiac mural thrombi. Finally, a majority of the patients already exhibiting thromboembolic phenomena would inevitably continue to suffer thromboembolic episodes with less and less hope of survival.

While some of the foregoing is conjectural, the fact remains that in none of the nineteen patients who recovered was there any evidence of extension of preexistent thrombus, arterial, intracardiac, or venous, once anticoagulation therapy was instituted. Furthermore, all thromboembolic processes were terminated promptly. When anticoagulation therapy with heparin/Pitkin menstruum was inaugurated early, there was suggestive delimitation of myocardial damage with more rapid clinical and electrocardiographic regression. In the optimally treated

patients, the span of bed rest was reduced conspicuously, the convalescence was accelerated, and the patients were restored more rapidly to their accustomed activities.

These patients presumably have an inherent clotting tendency and are subject to recurrent episodes of thrombosis. For this reason, after the intensive treatment for the acute thrombotic process has been completed, they are now given a maintenance prophylactic program with modest dosages of heparin/Pitkin menstruum while they are ambulatory and for an indefinite period of time. This prophylactic program was originally suggested by the ease with which heparinization was continued and accomplished for long periods of time in ambulatory patients who were up and about following severe venous thromboembolic disease. Patients were encountered repeatedly who required dosages of 300 to 400 mg. of heparin in the Pitkin menstruum every other day in order to effectuate adequate coagulograms during the active phases of the disease. These same patients, when there was no longer any detectable evidence of the persistency of thrombosis, could then be maintained in a protected state on as little as 100 mg. of heparin in the Pitkin menstruum deposited every second to seventh day or longer. This spacing permitted the patients to be treated as ambulatory subjects without inconvenience. There apparently is a direct relationship between the mass and extent of thrombosis and the degree of response to heparin; as the clots disappear, the individual becomes less resistant and more responsive to the anticoagulant. The detailed technical aspects of this program and the results of this prophylactic study will be the subject of a forthcoming report.

While expansion of this project to include a sufficiently large number of cases for statistical purposes is necessary to establish unequivocally the virtues of anticoagulation therapy in acute coronary artery thrombosis and its complications, the gratifying response of this small series of profoundly ill patients would seem to indicate that heparin/Pitkin menstruum, because of its simplicity of administration, prompt effectiveness, and absence of toxicity, is well suited for the treatment of this serious disease.

SUMMARY AND CONCLUSIONS

1. Anticoagulation therapy with heparin/Pitkin menstruum was the subject of an exploratory study in twenty consecutive, unselected patients with acute coronary artery thrombosis and myocardial infarction.

2. The treatment program and its rationale in acute coronary thrombosis is discussed.

3. All of the patients in the series were seriously ill; some were desperately ill. Fourteen of the patients (70 per cent) had clinically detectable, complicating thromboembolic episodes. One of these complicated cases represented the only treatment failure (5 per cent) in the series of twenty patients.

4. In none of the nineteen patients who recovered was there evidence of thrombus propagation, once anticoagulation therapy was instituted. Furthermore, all complicating thromboembolic processes were promptly terminated.

5. In the optimally treated patients the span of bed rest was conspicuously reduced. Convalescence was accelerated and the patients were restored more rapidly to their accustomed activity.

6. The gratifying response of this small, though representative series of gravely ill patients would seem to indicate that heparin/Pitkin menstruum, because of its simplicity of administration, prompt effectiveness, and absence of toxicity, is well suited for the treatment of acute coronary artery thrombosis and its complications.

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IV. CORRELATION OF ELECTROCARDIOGRAPHIC AND PATHOLOGIC FINDINGS IN INFARCTION OF THE INTERVENTRICULAR SEPTUM AND RIGHT VENTRICLE

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FROM pathologic studies, it is well known that infarction of the interventricular septum usually accompanies infarction of the free anterior wall of the left ventricle, often occurs in association with infarction of the free posterior wall, and occasionally develops as a primary lesion. Nevertheless, little or no attention has been devoted to the diagnosis of septal infarction in the current textbooks and monographs on electrocardiography. However, there are several reports of electrocardiographic studies in patients with pathologically proved or clinically presumptive septal infarction.

Auriculoventricular block is a well-documented complication of septal infarction. In a series of 375 cases of coronary occlusion, Master, Dack, and Jaffe[1] found prolongation of the P-R interval beyond 0.20 second in 10 per cent, second degree block in 2.4 per cent, and complete block in 1.6 per cent. The incidence of partial and of complete auriculoventricular block in this series corresponded closely with the averages in a group of 1,500 cases collected from the literature. High-grade partial and complete block were attributed to involvement of the auriculoventricular node secondary to infarction of the septum, but simple prolongation of the P-R interval could not be correlated with any specific anatomical lesion. The septal lesion responsible for severe auriculoventricular block was almost invariably associated with posterior infarction and only rarely represented an extension from anterior infarction. This finding corresponded with gross observation that the blood supply of the auriculoventricular node is derived from the right coronary artery in 92 per cent and from the left in 8 per cent of the hearts.

Prolongation of the QRS interval is another recognized manifestation of septal infarction. The incidence of this finding was 43 per cent in thirty patients with subsequent pathologic demonstration of infarction which extended into the septum, and was 21 per cent in nineteen patients with infarction which spared the septum.[2] However, an insufficient number of leads was obtained in these cases to localize accurately the conduction defect and thus to determine its relation to the anatomical lesions.

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Wilson and associates[3,4,5,6] demonstrated the need for multiple precordial leads for localization of the site of an intraventricular conduction defect and for the differentiation of defects due to septal infarction from those due to other causes. Conduction defects in the right side of the septum and right ventricle were recognized by the presence of a late intrinsicoid deflection in leads from the right precordium which faced these structures.[3] Right bundle branch block due to septal infarction was differentiated from that due to other causes by the direction of the initial phase of the QRS complex in these leads. Uncomplicated right bundle branch block was manifested by an initial R wave, a subsequent downstroke or coarse slurring, and a secondary late upstroke,[3] whereas right bundle branch block associated with septal infarction was characterized by an abnormal Q wave and a late R wave in these leads.[4,5,6] Section of the right branch of the bundle of His in dogs resulted in a primary and a secondary late R wave in leads from the right precordium, and subsequent septal infarction produced by ligation of the septal branch of the left coronary artery led to the replacement of the initial upstroke by an abnormal Q wave.[7] Thus, the initial R wave was derived from septal activation and was obliterated and replaced by a Q wave in the presence of extensive septal infarction.

Conduction defects in the left side of the septum and free wall of the left ventricle were recognized by the presence of an abnormally late intrinsicoid deflection in leads from the left precordium and axilla which faced these structures.[3] The site of the conduction defect in the left ventricle was indicated by the direction of the first phase of the QRS complex in these leads. When an initial R wave and late intrinsicoid deflection were recorded in left ventricular leads, the QRS prolongation was attributable to left bundle branch block.[3] This initial R wave persisted when left bundle branch block was complicated by anterolateral infarction. As a consequence, diagnostic signs of infarction were not present under these circumstances. When an abnormal Q wave and late intrinsicoid deflection were recorded in leads from the left precordium, the prolongation of the QRS complex was most likely due to delay in passage of the impulse through the free wall of the left ventricle secondary to infarction of the subendocardial portion.[6] However, QS deflections were recorded in left ventricular leads in one case of left bundle branch block as a result of the combination of a massive transseptal and extensive anterolateral infarction.[8]

The QRS interval may be of normal duration in the presence of extensive transseptal infarction, even when complicated by perforation of the septum.[9-12] Nevertheless, abnormalities in the QRS-T pattern suggestive or diagnostic of septal infarction may be detectable in precordial leads facing the right ventricle and right side of the septum in the absence of a conduction defect. The normal R wave in these leads is produced largely by activation of the septum and, partially, by activation of the outer wall of the right ventricle.[13,14] Kossmann and De La Chapelle[15] recorded QS complexes at positions over the right ventricle in a patient with anteroseptal infarction proved at necropsy and attributed the absence of the normal R wave from these leads to the lesion of the anterior portion of the septum. Pardee and Goldenberg[16] observed a transient QS complex and coronary T wave in Lead IVF in a case with infarction localized to the

anterior portion of the septum. Roesler and Dressler[17] reported five cases with pathologic evidence of extensive infarction of the septum, continuing into the anterior and posterior walls of the left ventricle. These were manifested electrocardiographically by signs of anterior infarction in the precordial and signs of posterior infarction in the limb leads. Their studies suggested that a diagnosis of infarction of the interventricular septum, as well as of the anterior and posterior walls of the left ventricle, may be made when the electrocardiogram reveals evidence of coexistent anteroposterior infarction.

In a previous communication,[18] two types of QRS pattern in right ventricular Leads V_1 and V_2 were correlated with the septal portion of an anteroseptal infarct found at autopsy, namely, (1) QS complexes which were shown to be abnormal rather than normal variants, either by the association of RS-T segment displacement typical of recent infarction or by the demonstration of an initial R wave in leads farther to the right, such as Lead V_{3R}; (2) an initial Q wave, followed by a small R wave and a deep S wave.

A similar method of electrocardiographic and pathologic examination is employed in the present study and all cases in which infarction was demonstrated at autopsy in one-third or more of the interventricular septum are included, except for thirteen cases of localized anteroseptal infarction summarized previously.[18] The material comprises six cases in which the infarction was primary in and largely confined to the septum, fifty-nine cases in which the septal lesion was associated with a large anterior or anteroposterior infarction, and twenty-four cases in which it was associated with posterior infarction. Significant septal involvement was thus found at autopsy in a total of 102 cases, or 63 per cent of the series of 161 cases upon which these reports are based. Eighteen cases are reported in detail in this communication and the findings pertaining to the septal lesion in the remainder are classified and summarized.

Continuation of infarction of the left ventricle and septum into the right ventricle is generally regarded as uncommon,[19,20] but was found in one-third of the cases by Bean[21] and by Feil, Cushing, and Hardesty.[22] Electrocardiographic patterns due to human right ventricular infarction have not been clearly defined, because of (1) the difficulty in differentiating the effects of the right ventricular extension from those of the primary left ventricular and septal lesion, and (2) the extreme rarity of infarction confined to the right ventricle. Electrocardiographic signs of posterior infarction were reported in three patients with subsequent pathologic demonstration of infarction limited to the right ventricle and septum.[22,23,24] In animals with experimental infarcts of the right ventricle, QS complexes and displacement of the RS-T segment were recorded in leads from the overlying epicardium,[25] which were similar to those registered through direct leads from the surface of a transmural left ventricular infarct. The reason for the obliteration of the initial upstroke of septal derivation in these animals was not apparent. Since septal infarction in human beings may be manifested by abnormal QS complexes and displacement of the RS-T segment in precordial leads over the right ventricle,[18] great difficulty would be anticipated in the electrocardiographic differentiation of septal and right ventricular infarction.

Isolated infarction of the right ventricle was not found in this series. Extension of infarction of the anterior wall of the left ventricle across the septum into the anterior wall of the right ventricle was demonstrated pathologically in six cases and continuation of a lesion of the posterior wall of the left ventricle into the posterior wall of the right ventricle was found in thirteen cases. These nineteen cases constituted 11.8 per cent of the entire series and will be analyzed to determine the presence or absence of electrocardiographic signs referable to the right ventricular involvement.

CASE REPORTS

CASE 69.—A 52-year-old man had had hypertension for seventeen years, but was asymptomatic until March, 1945, when he began to have dyspnea and transient epigastric fullness on exertion. He was admitted to the hospital in left ventricular failure on March 30 and promptly regained compensation. His clinical course was compatible with a small myocardial infarction. On Nov. 30, 1945, he was seized with severe protracted epigastric pain and was brought to the hospital in shock. He remained in circulatory collapse and died seven days later.

Electrocardiographic Findings.—Electrocardiograms from both admissions are reproduced serially in Fig. 1. The patient received 0.7 Gm. of digitalis prior to the electrocardiogram of March 31, an additional 1.9 Gm. between the first and second tracings, and 0.5 Gm. between April 9 and April 14. No cardiac glycosides were given during his second admission. All tracings taken during the first admission showed a QRS pattern typical of left ventricular hypertrophy and were characterized by a slurred R wave and late intrinsicoid deflection in Leads V_5 and V_6 and a deep, broad S wave in Leads V_1 and V_2. The coarse notching of the R wave in Lead V_4 was a transitional zone phenomenon. Attention is directed to the presence of an initial R wave in all precordial leads of each tracing on the first admission and to the absence of significant serial changes in the QRS pattern during this period. On the other hand, striking changes occurred in the RS-T segment and T wave in all precordial leads except Lead V_1. The initially inverted T waves in Leads V_5 and V_6 were less deep on April 9 and became low upright on April 14. The changes were opposite to those which would have been expected from progressive digitalization, but were compatible with those observed during recovery from left ventricular failure. The convexly upward bowing of the RS-T segment and the terminal inversion of the T wave in Leads V_2 through V_4 of the tracing of March 31 were strongly suggestive of a localized lesion in the mid-zone or subepicardial layer of myocardium and were probably independent of digitalis. A small anteroseptal infarct, a localized pericarditis, and acute right ventricular dilatation secondary to left ventricular failure were considered as possible causes of this pattern. The absence of T-wave inversion in Lead V_1 was strongly against acute cor pulmonale and the history was more in keeping with a very small infarct than with pericarditis. Serial changes occurred in the T waves of Leads I and II comparable to those in Lead V_6. Lead V_1 of the tracings taken during the second admission showed a tall R wave and a very late intrinsicoid deflection, beginning 0.10 second after the onset of the QRS complex, whereas Leads V_5 and V_6 exhibited a relatively early intrinsicoid deflection, beginning 0.04 second after the onset of the QRS complex, and followed by a broad, slurred S wave. These findings were diagnostic of right bundle branch block. A deep Q wave was found in Leads V_1 and V_2 in place of the initial R wave expected in leads over the right ventricle in the presence of right bundle branch block. Since this initial R wave is produced by activation of the septum, its disappearance and replacement by a Q wave constituted evidence of infarction of the septum. The initial Q wave in Lead V_1 represented left ventricular cavity potentials transmitted through the inert septum, and the tall late R wave was derived presumably from activation of an uninfarcted outer wall of the right ventricle over an aberrant pathway. The high voltage of the R wave was attributable to the circuitous route of activation and did not constitute evidence of right ventricular hypertrophy. The transitional zone was located near the midline in the tracing of December 1 and shifted to the left between Leads V_3 and V_4 on December 5. Thus, Leads V_3, V_4, and V_5 reflected the potential variations of the left ventricle,

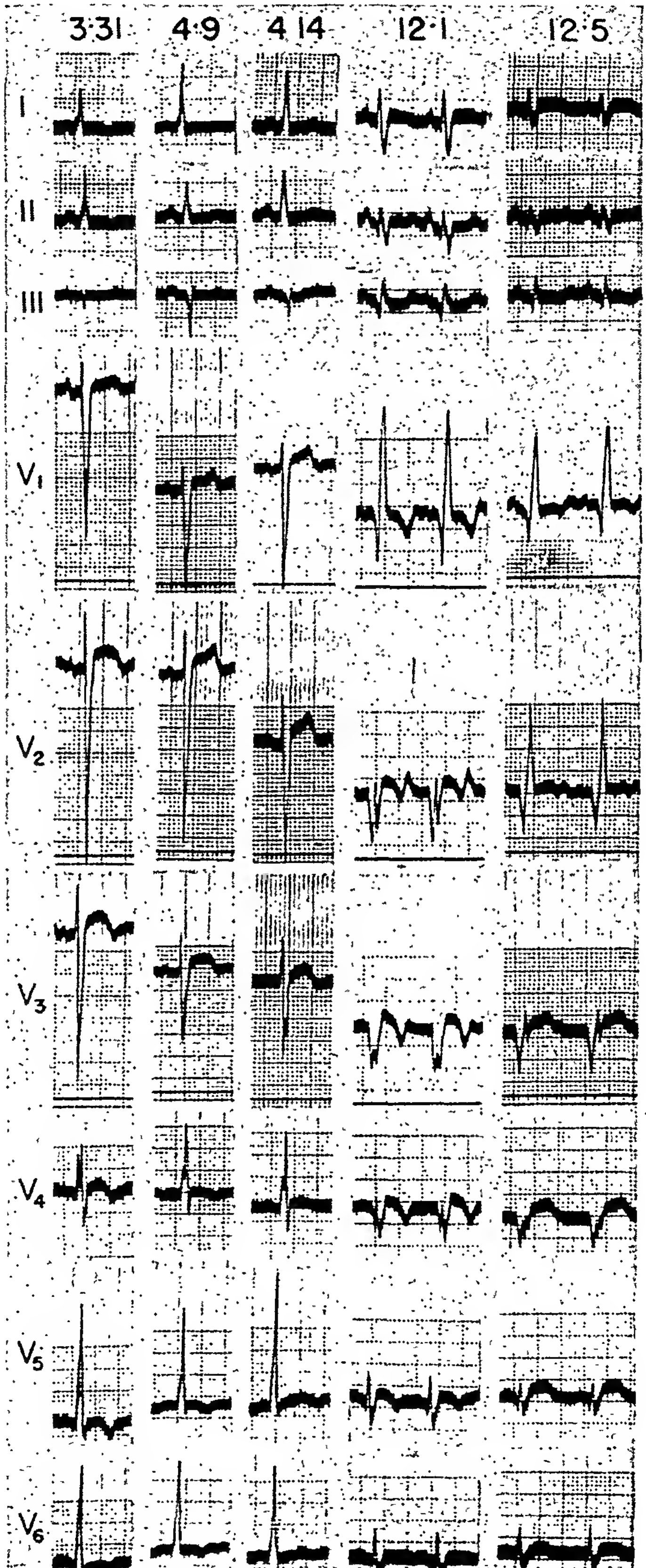

Fig. 1.—Serial electrocardiograms in Case 69, showing evidence of small intramural anteroseptal infarction in March and large anteroposterior and septal infarction with right bundle branch block in December.

and the abnormal Q wave and RS-T segment displacement in these leads were indicative of continuation of the septal infarct into the anterior and anterolateral walls of the left apex. The coved inverted T waves of Leads V_1 through V_5, recorded on December 1, were typical of recent infarction and their replacement by a monophasic upright T wave on December 5 was suggestive of further injury to the supepicardial layer. A triphasic QRS complex was recorded in Lead aV_F and could be resolved into Q, R, and S components, each of which was slurred and approximately 2.0 mm. in amplitude. In view of the presence of right bundle branch block, the late, broad S wave indicated that Lead aV_F reflected the potential variations of the posteroinferior wall of the left ventricle, and the abnormally broad, slurred Q wave signified extension of the infarct subendocardially into this region. The abnormal Q wave of Lead aV_F carried over into standard Leads II and III, producing a pattern in these leads of right bundle branch block complicated by posterior infarction.

Fig. 2.—Roentgenogram of the injected heart in Case 69, showing small, healed anteroseptal infarct in broken outline and recent anteroposterior and septal infarct in solid lines.

Pathologic Findings.—The heart weighed 641 grams and exhibited a recent comma-shaped infarct, which involved the entire apical two-thirds of the interventricular septum and extended forward into the subendocardial two-thirds of the anterior wall and backward into the postero-apical region, as demarcated by the solid lines of Fig. 2. The free wall of the right ventricle was not infarcted. There was a small healed infarct localized in the anteroseptal wall of the fifth segment, as indicated by the broken lines. An intramural infarct in this location could have accounted for the serial changes in the RS-T segment and T wave observed in Leads V_2, V_3, and V_4 during the first admission and for the absence of associated changes in the QRS complex. The location of the recent infarct corresponded closely with that predicted from the electro-

cardiograms taken on the second admission. It is noteworthy that a pattern customarily regarded as right bundle branch block accompanied an infarct which destroyed the apical two-thirds of the septum, but left the basal one-third intact. The expected initial R wave in right ventricular Lead V_1 was replaced by a Q wave, despite the presence of histologically normal muscle in the basal one-third of the septum. The initial positive potentials which might have been referred to the right ventricular cavity from activation of the intact portion of the septum were apparently obliterated by greater negative potentials simultaneously transmitted from the left ventricular cavity through the infarcted portion of the septum. The subendocardial position of the anterolateral infarct was accurately reflected in the Q-R pattern of Leads V_4 and V_5, and the subendocardial posteroapical infarct, by the Q-R complexes of Leads aV_F, II, and III.

CASE 70.—A 59-year-old woman gave a four-month history of uncontrolled diabetes mellitus. During this period she began to have angina pectoris. Attacks were of brief duration until the day of admission, when she had a prolonged attack of exceptionally severe retrosternal pain and was brought to the hospital in shock. A single dose of 2.0 cat units of Digalen was given shortly after admission. Death occurred on the seventh hospital day.

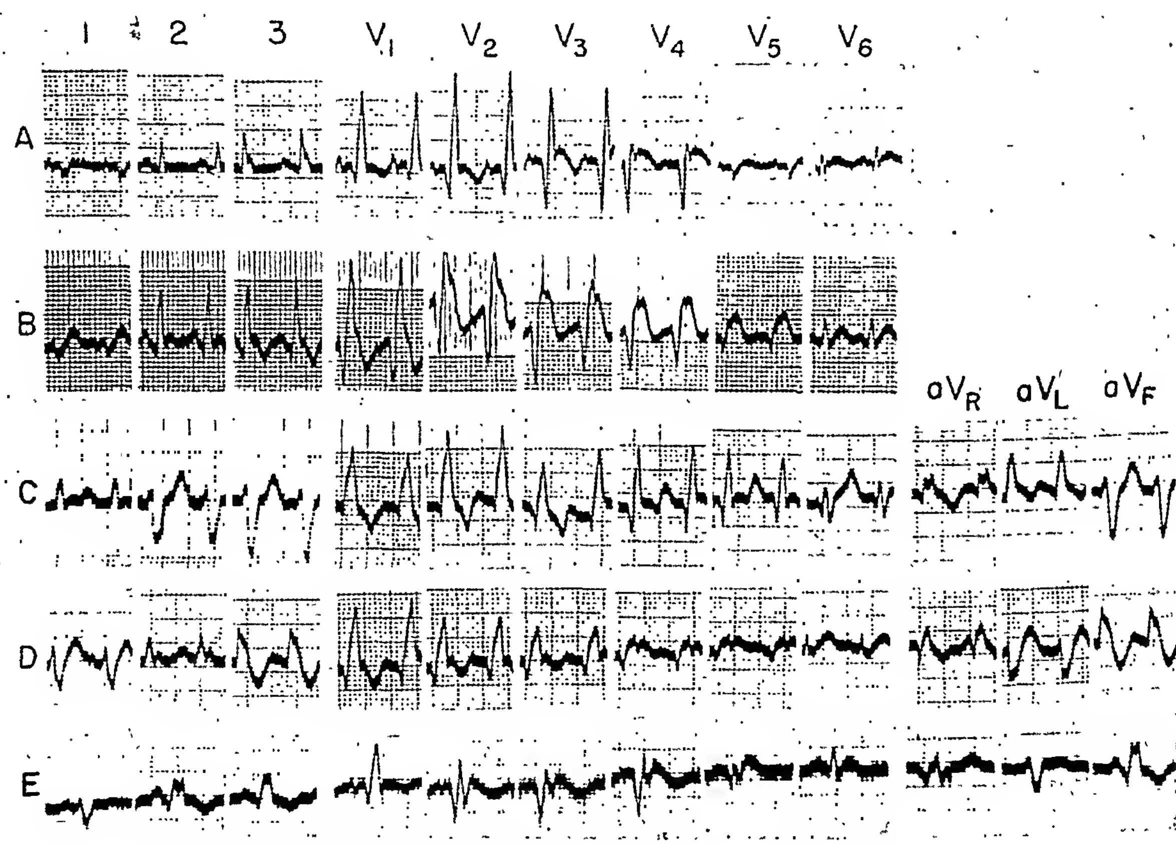

Fig. 3.—Right bundle branch block due to infarction of the interventricular septum. *A*, Case 70; *B*, Case 71; *C*, Case 72; *D*, Case 73; and *E*, Case 74.

Electrocardiographic Findings.—An electrocardiogram obtained on the fourth hospital day is reproduced in Fig. 3, *A*. The QRS pattern in tracings on the second and fifth days was comparable to that in the illustration. The tall R wave and late intrinsicoid deflection in Leads V_1 through V_3 were diagnostic of right bundle branch block, and the abnormal initial Q waves in the same leads, together with the elevated RS-T segment and inverted T wave in Lead V_3, indicated that the right bundle branch block was due to a recent infarction of the septum. The QR complex of Lead V_4 was probably transitional. The QS deflection and elevated RS-T segment in Lead V_5 constituted evidence of recent infarction of the anterolateral wall of the left

ventricle, and the triphasic QRS complex and dome-like RS-T segment in Lead V_6 were ascribed to extension into the lateral wall. The standard leads showed right bundle branch block, but no definite evidence of infarction.

Pathologic Findings.—The heart weighed 375 grams and exhibited a recent infarct which involved the entire septum and adjacent anteroseptal wall but did not extend into the lateral or posterior wall of the left ventricle, nor into the right ventricle. The distribution throughout the entire length of the septum and anterior wall of the ventricle was similar to that in the third and fourth segments in Case 69 (Fig. 2), except that the lesion of the outer wall was transmural. It is noteworthy that there was no significant difference between the precordial leads in this case and those obtained on December 5 in Case 69, despite the fact that the infarct extended through the entire length of the septum in this case, yet spared the basal one-third of the septum in the previous case. There was good correlation between the infarction of the septum and the abnormal Q waves associated with the pattern of right bundle branch block in Leads V_1, V_2, and V_3. The predicted involvement of the lateral wall was not borne out at autopsy. In view of the rather marked clockwise rotation of the heart, it is probable that the potential variations of the infarcted anteroseptal wall of the left ventricle were transmitted into the axilla to account for the abnormal Q waves in Leads V_5 and V_6.

CASE 71.—A 53-year-old man was perfectly well until a fortnight prior to hospital admission, when he had a number of attacks of transient retrosternal oppression. He was admitted in shock after thirty hours of continuous retrosternal pain and died thirty-four hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained twenty-six hours after admission and following the administration of quinidine in doses of 0.2 Gm. hourly during the four preceding hours is reproduced in Fig. 3, *B*. This electrocardiogram, as well as a previous tracing taken on the first hospital day, showed auricular flutter with a 2:1 A-V ratio. The tall late R wave in Leads V_1 through V_3 was indicative of right bundle branch block and the marked elevation of the RS-T segment and the terminal inversion of the T wave in these leads were diagnostic of recent myocardial infarction. Close scrutiny of the tracing in Leads V_1 through V_3 revealed a sharp upstroke about 1.0 mm. in height at the onset of the QRS complex. The portion of this upstroke that corresponded in width with the remainder of the QRS complex was considered part of the ventricular complex rather than the flutter movement, despite the fact that measurements of the QRS interval that included this upstroke were 0.03 second longer than measurements made in the limb leads. Thus, the findings in right ventricular leads in this case differed from those in Cases 69 and 70 in that the QRS complex began with a minute upstroke rather than with a prominent Q wave. There was a questionable minute initial upstroke in transitional Lead V_4. However, left ventricular Lead V_5 revealed an abnormal Q wave, markedly elevated RS-T take-off, and a monophasic upright T wave diagnostic of continuation of the septal infarct into the free anterior wall of the left ventricle. Lead aV_F displayed a Q wave 0.03 second in duration and 3.0 mm. in depth followed by a 12.0 mm. R wave. Although the R wave was comparable in amplitude to that in Lead V_1, it was derived from the posterior wall of the left rather than the right ventricle, as shown by the fact that the intrinsicoid deflection was 0.04 second earlier in Lead aV_F than in Lead V_1. The Q-R complex in Lead aV_F was carried over into Leads II and III and was interpreted as evidence of extension of the infarct subendocardially into the posterior wall of the left ventricle.

Pathologic Findings.—The heart weighed 388 grams and revealed a recent, large transmural infarct which involved the entire anterior wall and the apical half of the lateral and posterior walls of the left ventricle. The infarct extended through the entire apical half of the septum and the anterior portion of the basal half, crossing over to involve the anterior wall of the right ventricle, as indicated by the area of avascularity in Fig. 4. The right bundle branch block was presumably due to the septal infarction. In the event that the initial upstroke in Leads V_1 through V_3 was a part of the QRS complex, it might have constituted an indirect effect of the destruction of the entire anterior portion of the septum and adjoining anteroseptal wall of the left ventricle. The early arrival of the activating impulse in this portion of the heart is normally responsible for the

initiation of negativity in the left ventricular cavity. The complete infarction of this area may have delayed the development of significant negative potentials in the left ventricular cavity in this case until the impulse reached and began to activate the intact basilar half of the lateral and posterior walls. In the meantime, weak, positive potentials referred to the right ventricular cavity from activation of the posterobasal remnant of the septum may have preponderated over the negligible negative potentials available for transmission from the left ventricular cavity through the infarcted septum to the right side of the precordium. Under these circumstances, a minute initial R wave might have been recorded in nearby right ventricular Leads V_1 through V_3 without a simultaneous counterpart in the remaining more distant leads, thereby accounting for the discrepancy in measurements of the QRS interval. It is noteworthy that a definite RSR′

Fig. 4.—Roentgenogram of the injected heart in Case 71 with a large infarct of the anterior, lateral, and posterior walls of the left ventricle, the anterior wall of the right ventricle, and the septum, demarcated by its avascularity.

complex, along with abnormal displacement of the RS-T segment, was registered in Leads V_1 through V_3 in Case 54, as a manifestation of a somewhat smaller, but comparably placed, infarct. The extension of the infarct into the anterior wall of the right ventricle caused no demonstrable modification in the QRS complex, but might have contributed to the marked elevation of the RS-T segment in Leads V_1 through V_3. The massive, transmural anterolateral infarction adequately explained the QRS-T pattern in Lead V_5, but should have led to an abnormal Q wave in Lead V_6, as well. The Q wave in Leads aV_F, III, and II was a manifestation of the posteroapical extension of the infarct.

CASE 72.—A 55-year-old man, who had a past history of angina pectoris, awakened with very severe retrosternal oppression, following which he lost consciousness. He was brought to

the hospital in shock with an arterial blood pressure of 82/60 and inaudible heart sounds. Death occurred nine hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained two hours after admission is reproduced in Fig. 3, *C*. The second tracing, taken five hours later, showed no significant change in the QRS complex. In Leads V_1 through V_5, there was an initial downstroke followed by a tall upstroke with late peak. The Q wave increased at the expense of the R wave as the electrode was moved from Position V_1 to V_5. The tall R wave and the postponement of onset of intrinsicoid deflection to 0.08 second in V_1 and V_2 were indicative of right bundle branch block, and the initial Q wave pointed to infarction of the septum. Because of a comparable Q-R pattern in Leads V_3 through V_5 and a simultaneous intrinsicoid deflection, beginning 0.08 second after the onset of the QRS complex, it was concluded that Leads V_3 through V_5 also were reflecting the potential variations of the epicardial surface of the right ventricle and the infarcted septum. The quadriphasic RSR'S' complex of Lead V_6 was considered transitional. The T waves were sharply inverted in Leads V_1, V_2, and V_3, diphasic in Leads V_4 and V_5, and upright in Lead V_6. This relationship suggested that the transition in T waves occurred in Leads V_4 and V_5, distinctly to the right of the transition in the QRS complex. Although the small Q wave and tall, slurred R wave recorded in Lead aV_L might at first glance be regarded as left ventricular in origin, a comparison with the precordial leads showed that it corresponded much more closely with the pattern in right ventricular Leads V_1 through V_3 than with the findings in Lead V_6. This suggested that the potential variations of the right ventricle were referred to the left arm and those of the posterior aspect of the left ventricle, to the left leg. If this analysis of the precordial and Goldberger leads be correct, available tracings did not provide an adequate study of the anterior and anterolateral walls of the left ventricle. Thus, the only diagnosis justifiable from the electrocardiogram was that of a recent infarction of the interventricular septum. The standard leads showed a conduction defect, more suggestive of left than of right bundle branch block, but were not diagnostic of myocardial infarction.

Pathologic Findings.—The heart weighed 678 grams and exhibited left ventricular hypertrophy due to syphilitic aortic insufficiency. There was a very recent infarct involving the entire thickness of the interventricular septum, extending into the anterolateral wall of the left ventricle and across the septum into the anterior wall of the right ventricle. The position of the lesion was similar to that in Case 71 (Fig. 4), except that the posterior aspect of the left ventricle was spared. The right ventricle was markedly dilated, sufficiently so as to displace the transitional zone far to the left. It was believed that the Q-R pattern in Leads V_1 through V_5 was the result of the infarction of the interventricular septum, as recorded from the right ventricular side. Leads V_7 and V_8 would have been required for exploration of the left ventricle and for diagnosis of this portion of the infarct.

CASE 73.—A 38-year-old man gave a typical history of angina pectoris of three years' duration and of myocardial infarction, seven months previously. Within forty-eight hours of hospital admission he had two brief, but exceptionally severe, attacks of constrictive retrosternal pain. He was awakened by a third attack on the morning of admission and was brought to the hospital in shock. Death occurred sixteen hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained about four hours after the onset of the attack which necessitated hospitalization and fourteen hours before death is reproduced in Fig. 3, *D*. In Leads V_1 through V_3 there was a tall, slurred R wave and late intrinsicoid deflection, beginning 0.11 second after the onset of the QRS complex. These findings were diagnostic of right bundle branch block and the initial Q wave indicated underlying infarction of the interventricular septum. Leads V_6 and aV_L displayed a small initial R wave, an early intrinsicoid deflection, and a broad, slurred S wave. These findings were typical of those registered over the normal left ventricle in right bundle branch block, except for the unusually low voltage of the R wave. Leads V_4 and V_5 showed an abnormal Q wave followed by a peculiar M-shaped summit, which could be resolved into a broad, slurred R wave and an elevated RS-T junction. The small, but precipitous, downstroke of the notch was identified as the intrinsicoid deflection. Since this downstroke was synchronous with the intrinsicoid deflection of Leads V_1 through V_3 and much

later than that in Lead V_6, it was concluded that Leads V_4 and V_5 were reflecting the potential variations of the region overlying or immediately to the right of the septum. Thus, the transitional zone was displaced to the left between Positions V_5 and V_6. The abbreviation of the intrinsicoid deflection consequent upon the marked elevation of the RS-T segment in Leads V_4 and V_5 suggested that the septal infarct reached the epicardial surface. The initial notch of the QRS complex in Lead aV_F might have been a Q-wave equivalent, but was not sufficiently coarse for diagnostic inferences. The standard leads were typical of right bundle branch block, but revealed no definite evidence of recent infarction.

Fig. 5.—Roentgenogram of the injected heart in Case 73, showing old healed infarcts in broken outline and recent infarct of the anterior wall and septum in solid outline.

Pathologic Findings.—The heart weighed 465 grams and exhibited a recent infarct involving the entire septum and the adjoining anteroseptal wall of the left ventricle in the apical two segments and the anterior half of the septum and the adjoining subendocardial portion of the anteroseptal wall in the third segment, as demarcated by the solid lines of Fig. 5. It is noteworthy that a pattern consistent with right bundle branch block was apparently produced by an infarct confined to the apical half of the septum and that abnormal Q waves were recorded in right ventricular Leads V_1 through V_3, despite the fact that the basal half of the septum and the right ventricle were intact. Although abnormal Q waves in Leads V_4 and V_5 can usually be correlated with infarction of the anterolateral portion of the left apex, it was believed that this case constituted an exception. The fact that the time of onset of the intrinsicoid deflection of Leads V_4 and V_5 was similar to that of Leads V_1, V_2, and V_3 indicated that the Q waves of Leads V_4 and V_5, like those of Leads V_1 through V_3, were a manifestation of the septal rather than the left apical portion of the infarct. The involvement of the anteroseptal aspect of the left apex was missed

electrocardiographically because of the displacement of the transitional zone into the axilla. The low voltage of the initial R wave in Leads V_6 and aV_L might have been secondary to infarction of the free wall of the left ventricle, but diagnostic signs of this lesion were absent. An old patchy infarct of the basal portion of the anterior wall (represented by the broken lines in Fig. 5) was also obscured by the right bundle branch block. A separate patchy infarct of the posterior wall, also indicated by broken lines, was not evident electrocardiographically, probably because of transmission of the potential variations of the right ventricle to the left leg.

CASE 74.—A 62-year-old man had had angina pectoris for three years. Attacks were brief in duration until ten days before hospital admission, when he was seized with severe retrosternal pain which lasted three days. He arose from bed for the first time on the day of admission and collapsed on the street with a recurrence of retrosternal constriction and dyspnea. He was brought to the hospital in shock and died five days later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 3, *E*. Attention is directed to the similarity of this tracing to that obtained on December 1 in Case 69 (Fig. 1). The initial Q and tall R waves of Lead V_1, together with the delay in onset of the intrinsicoid deflection to 0.10 second, were indicative of right bundle branch block due to infarction of the interventricular septum. The slight elevation of the RS-T segment in Lead V_1 suggested that the septal lesion was of recent origin. Because of the broad S wave in all leads to the left of Lead V_1, it was concluded that the transitional zone was near the left sternal border and that Leads V_2 through V_6 reflected the potential variations of the anterolateral wall of the left ventricle. The abnormal Q wave and the upward displacement of the RS-T junction in Leads V_2 through V_6 were construed as evidence of continuation of the recent septal infarct into the anteroseptal and anterolateral aspects of the left apex. The small R and broad S waves of Lead aV_L represented the pattern recorded over the normal left ventricle in right bundle branch block and were probably transmitted from an uninfarcted basal portion of the lateral wall. From a first glance at Leads aV_F, II, and III, one might be tempted to attribute the abnormal Q wave in these leads to coexistent posterior infarction. However, the late intrinsicoid deflection in Lead aV_F indicated that this lead, like Lead V_1, reflected the potential variations of the right ventricle. Thus, the abnormal Q wave in Leads aV_F, II, and III, like that in Lead V_1, could have been produced by the septal infarction.

Pathologic Findings.—The heart weighed 430 grams and exhibited a recent infarct of the interventricular septum which extended into the anterolateral and posteroapical aspects of the left ventricle in a manner almost identical with that in Case 69 (Fig. 2). The right ventricle was uninvolved. The infarct of the anterior wall of the left ventricle was confined to the subendocardial one-half except in the apical segment, where it was transmural, and thus was well correlated with the findings in Leads V_2 through V_5. The entire interventricular septum was infarcted, not only in the first four segments, as in Fig. 2, but also in the basal segment, as well. This accounted for the abnormal QRS-T pattern in Leads V_1 and V_2. In addition to the extension of the acute infarct into the posterior aspect of the apical segment, there was an old, completely healed, patchy infarct occupying the basal three-fifths of the posterior wall of the left ventricle. Nevertheless, the abnormal Q wave recorded in Leads aV_F, II, and III was believed referable to the infarction of the septum rather than to the lesion of the posterior wall, for reasons already given.

CASE 75.—A 58-year-old man gave a typical history of angina pectoris, beginning two months before hospital admission, and was hospitalized in his first prolonged attack of retrosternal constriction. Despite strict confinement to bed, there were repeated attacks of retrosternal pain, usually relieved by nitrites and papaverine. Systolic and diastolic pressures were consistently subnormal. The patient suddenly died during a meal on the thirty-third day. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the twelfth hospital day is reproduced in Fig. 6, *A*. Right bundle branch block was established by the tall, coarsely slurred R wave and the 0.10 second interval preceding the intrinsicoid deflection in Lead V_1. A diagnosis of infarction of the septum was made from the presence of a Q wave instead of the expected initial

R wave in Lead V_1. The early attainment of the peak of the R wave (0.03 second after the onset of the QRS complex) and the broad, slurred S wave in Leads V_4 through V_6 represented the typical findings obtained through precordial leads over the normal left ventricle in cases of right bundle branch block. In Leads V_2 and V_3 the intrinsicoid deflection began after an interval of 0.07 and 0.06 second, respectively, and was followed by a definite S wave, which was not as broad as that in leads farther to the left. The pattern in Leads V_2 and V_3 was thus transitional between that of Leads V_1 and V_4, indicating that the electrode was in close proximity to the interventricular septum. The abnormal Q wave in Leads V_2 and V_3 constituted further evidence of septal infarction. The significant difference between the precordial leads in this case and in the majority of the six preceding cases lay in the absence of Q waves from leads over the anterolateral aspect of the left ventricle (Leads V_4 through V_6). This was interpreted as evidence that this septal infarct did not extend into the anterolateral aspect of the left apex. The resemblance of the QRS complex in Lead aV_F to that in Lead V_6 signified that the potential variations of the left ventricle were transmitted to the left leg. The small W-shaped QRS complex of Lead aV_L was regarded as a transitional complex, transmitted from the neighborhood of the interventricular septum, due to semivertical position of the heart. The QRS complexes in three other tracings taken during hospitalization were essentially the same as in the electrocardiogram reproduced in Fig. 6, *A*. Over this period the T waves in Leads V_1 through V_3 showed gradually increasing depth associated with the organization of a recent infarct. The standard leads showed right bundle branch block, but were not diagnostic of infarction, either in single or serial tracings.

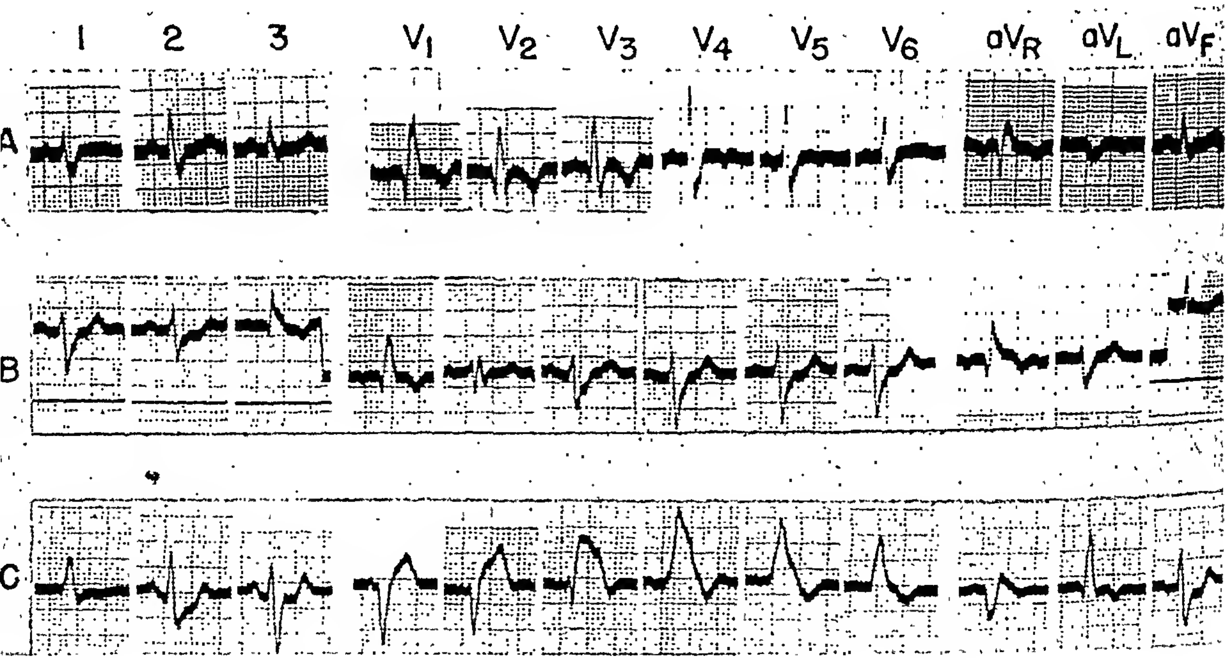

Fig. 6.—Primary septal infarction. *A*, Case 75; *B*, Case 76; *C*, Case 77.

Pathologic Findings.—The heart weighed 563 grams and exhibited left ventricular hypertrophy and right ventricular dilatation. An organizing infarct occupied the greater portion of the interventricular septum and extended into the anteroseptal wall of the mid-portion of the left ventricle, as represented by the solid lines in Fig. 7. On gross inspection the infarct appeared to be limited to the left ventricular half of the septum, but on microscopic examination it extended in patchy fashion to the endocardium of the right side of the septum. The broken lines projecting posteriorly represented an older area of patchy subendocardial infarction, which was continuous in the septum with the more recent infarction. Despite the fact that the infarct was much denser in the left then in the right half of the septum, the conduction defect involved the right rather than the left bundle branch. The localization of the abnormal Q waves to right

ventricular Lead V_1 and to transitional zonal Leads V_2 and V_3 conformed closely with the limitation of the infarct to the septum and subendocardial portion of the adjacent anteroseptal wall. The absence of infarction of the anterolateral wall in the apical two segments could be correlated with the normal initial phase of the QRS complex in Leads V_4 through V_6 and confirmed the ante-mortem interpretation of Lead aV_L. The older infarct of the subendocardial portion of the posterobasal wall was not demonstrable by electrocardiogram.

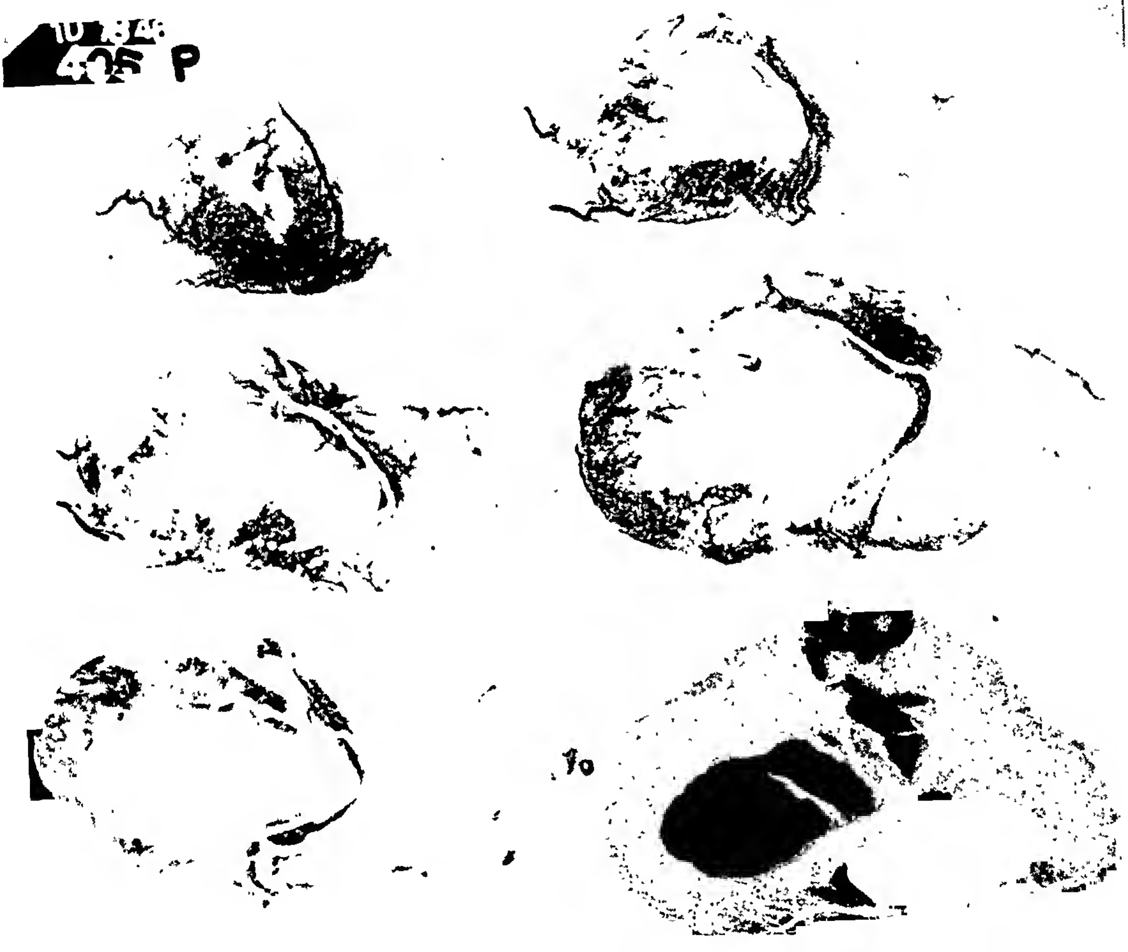

Fig. 7.—Roentgenogram of the injected heart in Case 75, showing recent septal infarct in solid lines and old, healed posterior infarct in broken lines.

CASE 76.—A 77-year-old hypertensive woman had been free of cardiovascular symptoms until four days before admission to the hospital, when she was suddenly seized with severe epigastric pain, accompanied by dyspnea and extreme prostration. She was admitted in severe congestive heart failure and circulatory collapse and died four hours later. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained one hour after admission is reproduced in Fig. 6, *B*. The prominent slurred R wave in Lead V_1 and the interval of 0.09 second preceding the onset of the intrinsicoid deflection in this lead were indicative of right bundle branch block. The early onset of the intrinsicoid deflection in Leads V_3 through V_6 and the subsequent broad, slurred S wave represented the typical pattern registered through precordial leads over the left ventricle in cases of right bundle branch block. Because of the normal initial phase of the QRS complex in these leads, it was concluded that the anterior wall of the left ventricle was

not infarcted. A diagnosis of septal infarction was strongly suggested by the initial Q wave in Lead V_1, but was not supported by the findings in Lead V_2. The latter was apparently a transitional lead recorded from a point in the vicinity of the septum and showed an initial R wave rather than the Q wave to be expected if the septum were infarcted. A diagnosis of infarction of the muscle immediately beneath the endocardium of the right side of the septum was suggested by the elevation of the RS-T junction in Lead aV_R. Because of the transmission of potential variations of the endocardial surface of the right side of the septum to the right ventricular cavity and thence to the right arm, injury to the muscle immediately beneath this portion of the endocardium might cause displacement of the RS-T segment in Lead aV_R analogous to that produced in Lead aV_L by injury to the subepicardial muscle of the lateral wall of the left ventricle. However, caution was also needed in making diagnostic inferences from the high RS-T take-off in Lead aV_R, since we have observed greater elevation in this lead in a case of right bundle branch block associated with hyperpotassemia, but without pathologic evidence of myocardial infarction. Thus, in the ante-mortem interpretation, the tracing was considered strongly suggestive, but not pathognomonic, of infarction limited to the septum. The small Q wave in Lead III was of no significance because inspection of the Goldberger leads showed that it was derived from initial positivity of the left arm rather than initial negativity of the left leg.

Pathologic Findings.—The heart weighed 590 grams and revealed a recent comma-shaped infarct, extending through the septum in the second, third, and fourth segments in a fashion almost identical with the lesion in the second and third segments in Case 83 (Fig. 15). This infarct continued for a distance of 1.0 cm. into the subendocardial half of the adjoining anterior wall of the left ventricle. The remainder of the free wall of the left ventricle and the entire outer wall of the right ventricle were intact. The disproportion between the relatively small infarct at autopsy and the severe congestive failure and circulatory collapse during life is noteworthy. The Bernheim syndrome could not be demonstrated at autopsy and no other cause for death was found. The initial Q wave of Lead V_1 was regarded as a manifestation of the septal infarct and the initial R wave in transitional Lead V_2 was best explained by the assumption that the potential variations of the electrode were dominated by those of the uninfarcted anterior wall of the left ventricle, just to the left of the septum. The normal initial phase of the QRS complex in Leads V_3 through V_6 was well correlated with the absence of pathologic evidence of infarction of the anterolateral wall of the left ventricle. The elevation of the RS-T segment in Lead aV_R was probably due to the septal infarction, and the slight depression of the RS-T segment in Leads V_4 and V_5 may have been a reciprocal effect.

CASE 77.—A 71-year-old man had been perfectly well until the morning c dmission to the hospital, when he was suddenly seized with severe oppressive pain in the precordium, radiating into the left shoulder and arm, accompanied by marked dyspnea and followed by syncope. He was brought to the hospital in profound collapse with unobtainable blood pressure and died twelve hours later.

Electrocardiographic Findings.—An electrocardiogram taken four hours after the onset of pain and eleven hours before death is reproduced in Fig. 6, *C*. The pacemaker shifted between the sinus and A-V node. The striking feature of the precordial leads was the extreme elevation of the RS-T segment in Leads V_3 and V_4 and the less marked, but definitely abnormal, elevation in Leads V_1, V_2, and V_5. The displacement of the RS-T segment in Leads V_3 and V_4 was greater than is observed in pericarditis and was considered diagnostic of very recent anterior infarction. The presence of an initial R wave in all precordial leads was an unusual finding, but might be associated with acute anterior infarction under the following circumstances: (a) Limitation of the infarct to the subepicardial layer of the anterior wall, or (b) presence of a very patchy lesion, which spared the major portion of the myocardium. (Neither of these possibilities could scarcely have explained the profound shock and early death.) (c) Complicating left bundle branch block, or (d) infarction of subendocardial layer of the left side of the septum, which destroyed the Purkinje network rather than the left bundle branch. Either left bundle branch block or destruction of the left side of the septum should reverse the vector associated with septal activation, with consequent reference of negative potentials to the right ventricular cavity and positive potentials

to the left ventricular cavity. Both of these possibilities warranted consideration, in view of the contour of the QRS complex in Leads V_4, V_5, and V_6 and the QRS interval of 0.13 second in these leads. However, the S wave in Leads V_1, V_2, and V_3 was not as broad as would be expected under these circumstances and the distinct Q wave preceding the tall R wave of Lead aV_L was difficult to reconcile with either alternative. (c) A very early transmural infarct, too brief in duration for obliteration of the response to the activating impulse, was in keeping with the short interval between the onset of the pain and the recording of the electrocardiogram and seemed the best explanation for the abnormally prolonged R wave in Leads V_4 through V_6, and the broad Q wave in Lead aV_L. The depression of the RS-T segment in Lead aV_F was considered reciprocal to the elevation in leads over the anterior wall of the left ventricle. This depression was carried over into Leads II and III. The pattern in the standard leads was abnormal, but was not characteristic of an infarction.

Fig. 8.—Roentgenogram of the injected heart in Case 77.

Pathologic Findings.—The heart weighed 506 grams and exhibited a brownish discoloration of the left side of the anterior two-thirds of the septum and the adjacent anterolateral wall of the mid-portion of the left ventricle, as outlined in Fig. 8. Multiple microscopic blocks revealed a very recent infarct extending through the entire thickness of the anterior wall and septum in the area outlined. The subepicardial portion of the acute anterolateral infarct presumably accounted for the marked elevation of the RS-T segment. The septal lesion did not extend high enough to have reached the left bundle branch. Since the entire thickness of the septum was infarcted, the hypothesis of an initial R wave in the precordial leads produced by activation of the septum

from right to left did not seem very likely. On the whole, the recording of an initial upright, rather than a downward, deflection in Leads V_4, V_5, and V_6 was best explained by the supposition that the lesion was too early for complete obliteration of the response to the activating impulse.

Case 78.—A 60-year-old man gave a four-month history of repeated attacks of typical anginal pain. These attacks came at rest, as well as on exertion, and generally lasted from five to thirty minutes until Jan. 21, 1947, when a prolonged attack of exceptionally severe pain occurred which necessitated hospitalization. Physical examination revealed syphilitic aortic insufficiency and severe congestive heart failure, necessitating maintenance on digitalis throughout hospitalization. On the morning of January 29 he was found in shock with a rapid, totally irregular ventricular rhythm. Quinidine was instituted and continued in a dose of 0.25 Gm. every four hours for the remainder of his hospital stay. A pericardial friction rub was heard for the first time on January 30. Death occurred on Feb. 2, 1947.

Electrocardiographic Findings.—Electrocardiograms selected from a series obtained during his thirteen days of hospital stay are reproduced in Fig. 9. On January 24 sinus rhythm was present. On January 30 there was an auricular tachycardia with auricular rate of 230, usually with variable ventricular response, but with intermittent 2:1 ratio, as seen in Lead V_2. On February 1 there was a wandering pacemaker between sinus and A-V nodes, well brought out in Lead II. The disturbance in auricular rhythm which developed on January 29 raised the question of extension of an infarct into the atria. The pattern of the QRS complex in the standard leads was fairly typical of left bundle branch block and was quite constant throughout, except for lengthening in QRS interval from an original measurement of 0.14 to 0.16 second. Although minor changes were observed in the T waves in the standard leads, there were no findings in these leads which were considered diagnostic of recent infarction. On the other hand, the precordial leads showed definite signs of recent infarction and furnished evidence of a different type of conduction defect from that postulated from the standard leads. In Lead V_6 there was an initial R wave, which reached its peak within 0.04 second, and a subsequent broad, slurred S wave, strongly suggestive of right bundle branch block. At first glance, the QRS complex of Leads V_1 through V_3 appeared to consist solely of a downward deflection; however, the time interval, as measured from the beginning of the QRS complex in Leads V_1 through V_3 to the end of the steep upstroke, was only 0.10 second, whereas the duration of the QRS complex, as measured in both the standard leads and Lead V_6, was 0.14 second. More careful scrutiny of Leads V_1 through V_3 revealed an elevated, slurred plateau which, from measurements, was considered part of the R wave, the RS-T junction being marked by a slight dip. The findings in Leads V_1 through V_3 were transmitted from the right, rather than the left, side of the heart, as evidenced by the diphasic P waves, indicating proximity of the electrode to the right atrium and by the later attainment of the peak of the R wave in these leads than in Lead V_6. Thus, the late, broad, slurred R wave detected by careful scrutiny of Leads V_1 through V_3 established the presence of right bundle branch block, and the initial Q wave in these leads was indicative of infarction of the interventricular septum. The pattern in Leads V_4 and V_5 differed significantly both from that in Leads V_1 through V_3 and from that in Lead V_6. Although the transitional zone in right bundle branch block may be displaced as far to the left as V_4 or V_5, the late R wave derived from the delayed activation of the outer wall of the right ventricle attains its maximum in Lead V_1 or V_2 and diminishes as the electrode is moved farther to the left. Thus, it was concluded that the late R wave in Leads V_4 and V_5 was of left, rather than right, ventricular origin. The normal P-R interval indicated that left, as well as right, bundle branch block could not be present, and the 0.04 second interval between the onset of the QRS complex and the beginning of the intrinsicoid deflection in Lead V_6 also excluded complete left bundle branch block. The initial Q wave and the subsequent prolonged slurred ascending limb of the R wave and postponement of the intrinsicoid deflection to 0.08 second in Leads V_4 and V_5 indicated that the conduction defect was in the anterolateral aspect of the outer wall of the left ventricle. From the Q-R pattern in Leads V_4 and V_5, together with the elevated RS-T junction and cove-shaped inversion of the T wave in Lead V_4, a diagnosis was made of anterolateral infarction, dense in the subendocardial layer and patchy in the mid-zone and subepicardial layer. The late R wave in Leads V_1 and V_2, due to right bundle branch block, increased greatly in amplitude in the tracing of February 1, and the transitional zone shifted to

the left. A Q wave appeared in Leads V_6 and aV_L, which, together with the elevation of the RS-T junction in Leads V_4 through V_6, suggested extension of the infarct farther into the lateral wall of the left ventricle.

Pathologic Findings.—The heart weighed 719 grams, as a result of left ventricular hypertrophy from syphilitic aortic insufficiency. There was a large horseshoe-shaped infarct, occupying the subendocardial half of the anterior and lateral walls of the left ventricle and the interventricular

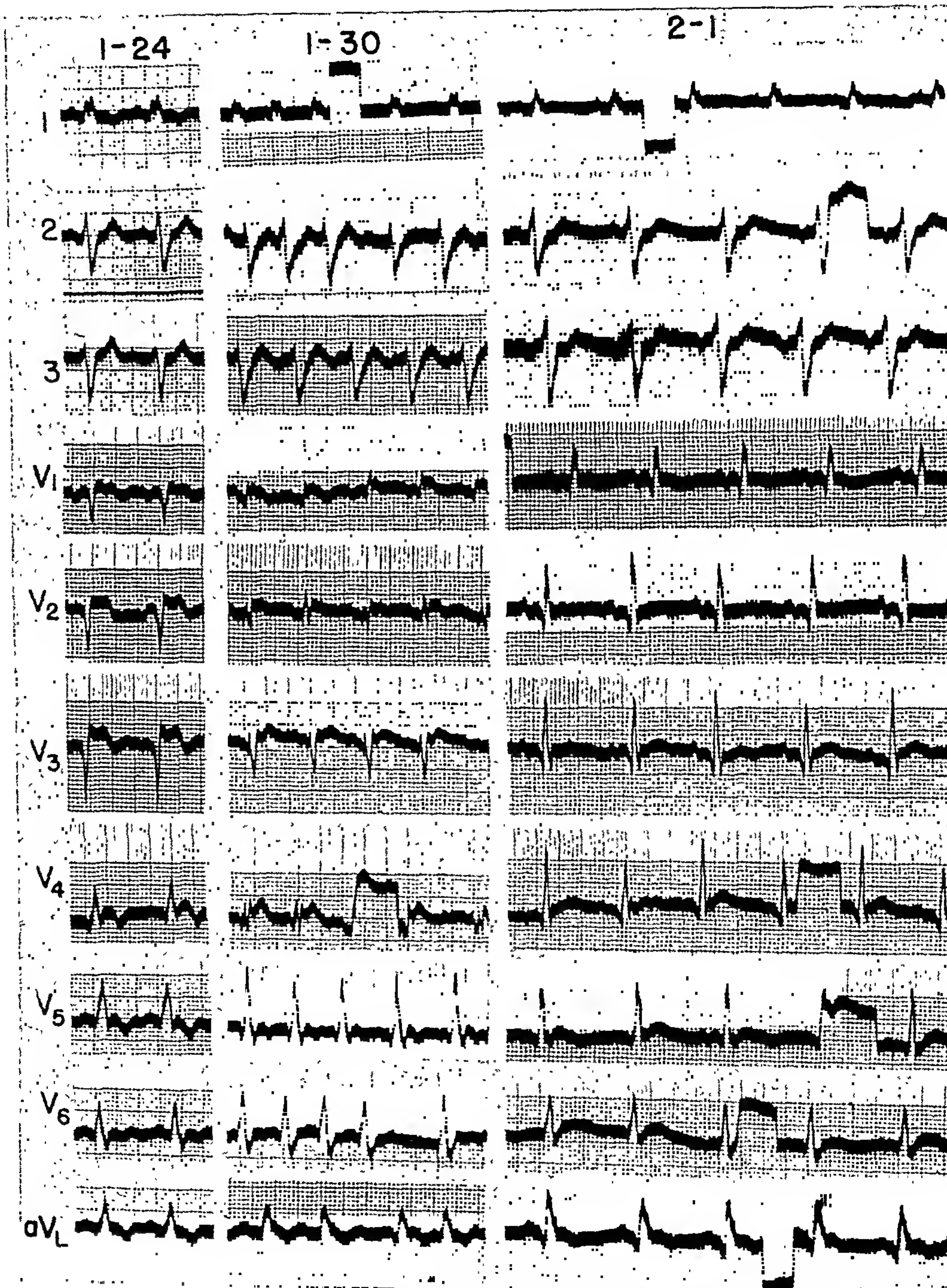

Fig. 9.—Serial electrocardiograms in Case 78.

septum in all segments. The area of involvement in each of the six segments was similar to the avascular portion of the second segment of Fig. 11, which represents the roentgenogram of the heart in Case 79. The outer wall of the right ventricle was intact. The infarction of the interventricular septum was deemed responsible for the right bundle branch block and the abnormal Q-wave pattern in Leads V_1 and V_2 and probably in Lead V_3. Sections through the anterior wall showed patchy fibrosis, which was presumably a remnant of the numerous episodes of coronary insufficiency and, in addition, revealed an organizing infarct, which was fairly dense in the subendocardial half, but very patchy in the subepicardial half. The age and distribution of the organizing infarct satisfactorily accounted for the abnormal initial Q wave and delayed peak of the R wave in Leads V_4 and V_5. Sections from the lateral wall showed a similar patchy fibrosis and, in addition, a fairly dense subendocardial infarct of two to four days' duration. This lesion could be correlated with the serial changes in the QRS-T pattern in Leads V_5, V_6, and aV_L. An organizing mural thrombus was found in the right auricle, but unfortunately no microscopic sections were taken to settle the question of atrial infarction.

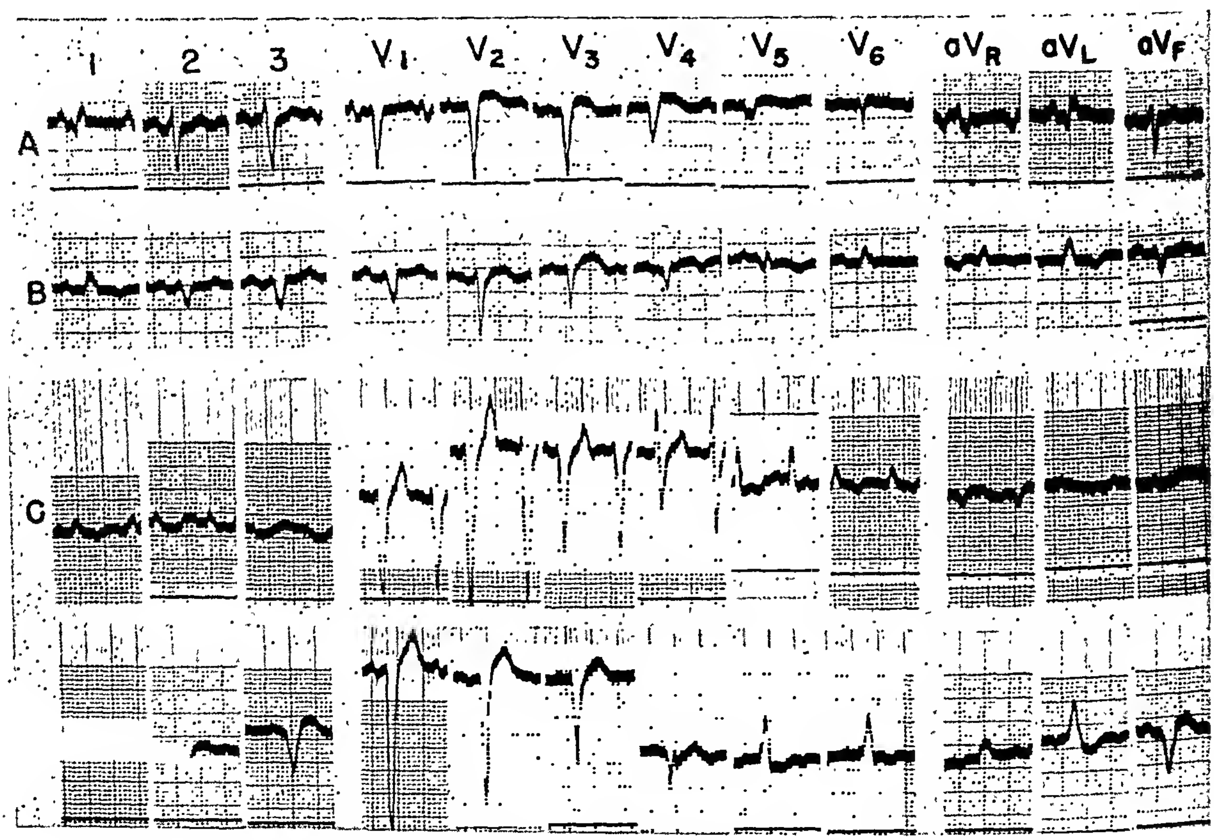

Fig. 10.—Infarction of the septum and anterior wall of the left ventricle. *A*, Case 79; *B*, Case 80; *C*, Case 81; *D*, Case 82.

CASE 79.—A 71-year-old man was admitted to the hospital moribund, one and one-half hours after the sudden onset of extreme orthopnea, not accompanied by chest pain. Past history was negative, except for exertional dyspnea of six weeks' duration. He made a dramatic response to therapy, which included 1.6 mg. of Cedilanid intravenously, and was quite comfortable until the ninth day, when there was a recurrence of dyspnea, accompanied by shock. He rallied following redigitalization, but died suddenly on the twelfth day.

Electrocardiographic Findings.—An electrocardiogram obtained twenty-three hours after admission is reproduced in Fig. 10, *A*. The finding of a small, but definite, initial R wave in Lead V_1, a QS complex in Leads V_2 through V_4, a W-shaped QRS complex of low voltage in Leads V_5

and V_6, and an abnormal QR complex in Lead aV_L was diagnostic of a large transmural infarct of the anterior and anterolateral walls of the left ventricle, becoming subendocardial farther in the lateral wall. The contour of the RS-T segments and T waves in Leads V_2 through V_4 was suggestive of recent infarction. The QRS interval of 0.12 second was indicative of a conduction defect and the abnormal Q wave in precordial leads over the left ventricle and in Lead aV_L, together with the notched late R wave of Lead aV_L, constituted strong evidence that the conduction defect was located in the free wall of the left ventricle. If left bundle branch block had been responsible for the QRS prolongation, an initial R wave would have been expected in left ventricular leads, because of early positivity of the left ventricular cavity, resulting from activation of the septum from right to left. The registration of an abnormal Q wave in leads over an anterolateral infarct is possible in the presence of left bundle branch block, if the entire septum, or the major portion of it, is unresponsive because of infarction. Under these circumstances, the left ventricular cavity might become initially negative, because of potentials derived from the activation of the outer wall of the right ventricle and transmitted through the inert septum, and would subsequently show increasing negativity as the impulse reached and activated uninfarcted portions of the outer wall of the left ventricle. The combination of complete infarction of the septum and bundle branch block was considered very remote in this case, because the QRS interval should have been considerably greater than 0.12 second under those conditions. Standard Lead I was also diagnostic of anterolateral infarction.

Fig. 11.—Roentgenogram of the injected heart in Case 79 with large anterolateral and septal infarct, demarcated by its avascularity.

Pathologic Findings.—The heart weighed 598 grams and exhibited a large transmural infarct, represented by the avascular areas in Fig. 11. In the apical segment, this lesion occupied the circumference of the left ventricle; in the second and third segments it involved the entire anterior wall and the anterior one-half to one-third of the lateral and septal walls and extended across the latter to include a narrow strip of the adjoining right ventricle; in the fourth segment it was confined to the anteroseptal aspect of the left ventricle. The anterior wall of the left ventricle

in the apical three segments was actually only 5.0 mm. in thickness. The remainder of the roentgenographic shadow consisted of mural thrombus, which completely filled an aneurysmal sac created by the herniation of the anterior wall. Microscopic examination revealed an old, patchy anteroseptal infarct estimated to be about two months in duration with a superimposed organizing infarct of the anterior, lateral, and septal walls estimated to be about two weeks in duration. The conduction defect was probably located in the incompletely infarcted lateral wall rather than the septum, because of the moderate prolongation of the QRS complex, the abnormal Q-wave pattern in all leads facing the anterolateral wall, and the absence of infarction of the basal half of the septum at autopsy. The septal and right ventricular portions of the infarct were not evident electrocardiographically. The possibility that the extension into the septum and anterior wall of the right ventricle might have occurred during the attack on the ninth hospital day was not supported by the pathological evidence. There was good correlation between the findings in Leads V_2 through V_6 and aV_L and the infarction of the anterolateral wall found at autopsy. The extension into the posterior aspect of the apical segment was not diagnosed ante mortem, probably because of horizontal position of the heart.

CASE 80.—A 79-year-old woman entered the hospital because of a fractured femur, which was treated by surgical reduction. Three days postoperatively she complained of a sudden sense of impending death, which was not accompanied by actual pain. Congestive failure ensued and persisted until death twenty days later.

Electrocardiographic Findings.—An electrocardiogram obtained nine days after the onset of the sense of impending death and following the administration of 0.6 Gm. of digitalis is reproduced in Fig. 10, *B*. A diagnosis of recent anterolateral infarction was made from the abnormally reduced initial R wave and dome-like elevation of the RS-T segment in Lead V_3, together with the QR complexes and cove inversion of the T waves in Leads V_4 and V_5. Several other tracings taken from four to eighteen days after the onset of the present illness showed a comparable QRS pattern, together with the usual RST-T evolution found in recent organizing anterolateral infarction. The question arose as to the site of the conduction defect responsible for prolongation of the QRS interval to 0.12 second. Left bundle branch block was suggested by the broadened, slurred initial R wave recorded in Leads V_6, aV_L, and I. To reconcile the association of left bundle branch block with the presence of Q waves in left ventricular Leads V_4 and V_5, it was necessary to postulate that the anterior infarct had involved the entire septum or the major portion of it. Destruction of the septum would be expected to eliminate the customary initial positivity of the left ventricular cavity resulting from aberrant septal activation in left bundle branch block, thereby making possible the registration of a Q wave in leads overlying an anterolateral infarct, as discussed in connection with Case 79. However, the circuitous route of left ventricular activation necessitated under these conditions should have caused greater prolongation of the QRS interval. For this reason, serious consideration was given to an alternative explanation for the QRS pattern in Leads V_6, aV_L, and I, namely, a very patchy transmural infarction of the lateral wall. Such a lesion might cause sufficient delay in the passage of the impulse through the lateral wall to cause prolongation of the QRS complex to 0.12 second and sufficient reduction in electromotive force to account for the low voltage of the R wave. Because of the similarity of the slurred R wave recorded in Lead aV_R to that in aV_L, it was probable that the heart was rotated backward on its transverse axis, thereby facilitating transmission of the potential variations of the posterobasal aspect of the left ventricle to both upper extremities.

Pathologic Findings.—The heart weighed 567 grams and showed a very large organizing infarct, involving the entire apical two-thirds of the septum and the anterior part of the basal one-third, along with most of the anterior wall of the left ventricle, the apical one-half of the lateral wall, and the apical one-third of the posterior wall. The distribution of the lesion in the left ventricle was almost identical with that in Case 71 (Fig. 4), but the right ventricle was spared in the present case. The infarct involved the entire thickness of the anterior and anterolateral walls, but was patchy in distribution, which apparently accounted for the small late R wave of Leads V_4 and V_5 and the reduced initial R wave of Lead V_3. The patchy infarct of the lateral wall of the left ventricle could have accounted for both the low voltage and slurring of the R wave

in Leads V_6 and aV_L and seemed a better explanation for the 0.12 second interval of the QRS complex than left bundle branch block complicated by septal infarction. However, the latter alternative could not be definitely excluded, since it is possible that activation of the small intact remnant of the septum might have occurred from right to left (as a result of left bundle branch block) without producing positive potentials of sufficient magnitude for the registration of an initial R wave in left ventricular leads.

CASE 81.—A 74-year-old man, who had been under treatment elsewhere for peptic ulcer, was suddenly stricken with severe midepigastric pain, accompanied by shortness of breath and followed by delirium. He was admitted to the hospital in circulatory collapse and died on the ninth hospital day.

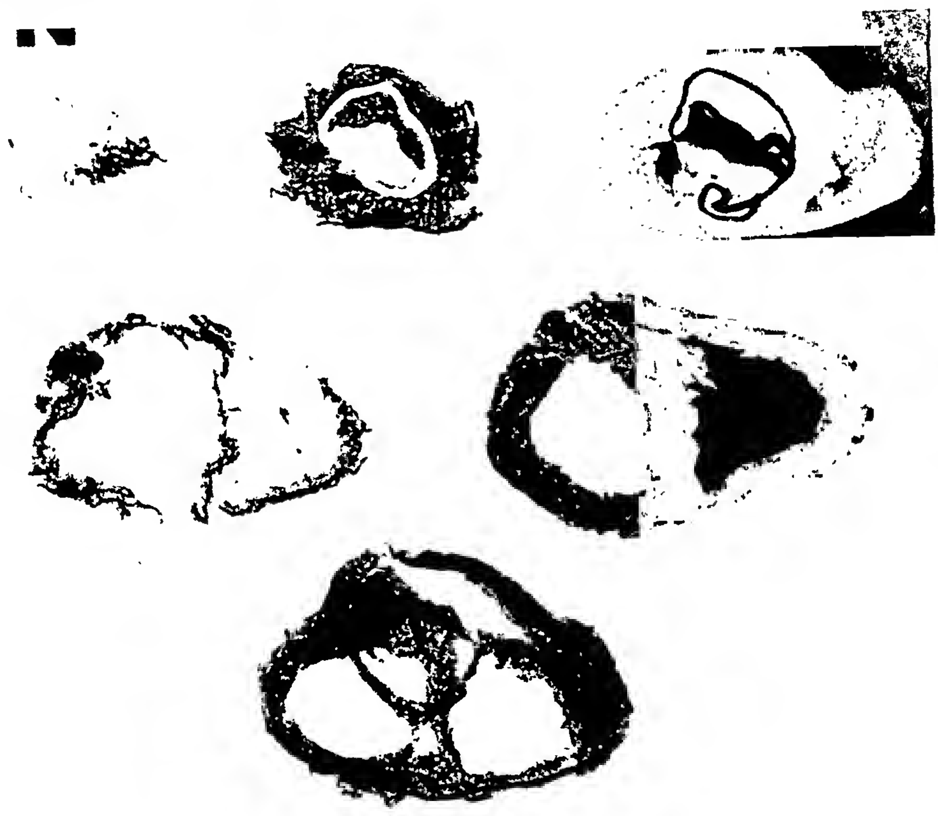

Fig. 12.—Roentgenogram of the injected heart in Case 81, showing position of the infarct in the septum and the subendocardial portion of the anterior and posterior walls.

Electrocardiographic Findings.—An electrocardiogram obtained five days after the onset of sudden epigastric pain and before the administration of digitalis is reproduced in *Fig. 10, C.* The initial phase of the QRS complex was upright in all precordial leads, in Lead aV_L, and in Lead aV_F. The R wave was of borderline amplitude in Lead V_5 and was of abnormally low voltage in left ventricular Lead V_6, aV_L, and aV_F and in the standard leads. However, a broad, deep S wave of left ventricular origin was recorded in Leads V_1 and V_2. This suggested that the low voltage in axillary and limb leads may have been due to an extracardiac cause, such as emphysema. The QRS interval, as measured in Leads V_1, V_2, and V_3, was 0.12 second. The broad, slurred R wave in left ventricular leads and widened S wave in right ventricular leads indicated that the conduction defect was situated in the left ventricle and the presence of an initial upright deflection in all leads over the left ventricle pointed to left bundle branch block. Attention is directed to the fact that the initial R wave in Leads V_1 and V_2 measured 2.0 to 3.0 mm. and fell off to 1.0 mm. in

Lead V_3. This was abnormal and raised the question of patchy anteroseptal infarction, but, in the ante-mortem interpretation, was not considered sufficiently decisive to permit a definite diagnosis. The upright T waves in Leads V_1 through V_4 and the depressed RS-T junction and inverted T waves of Leads V_5 and V_6 were compatible with those encountered in left bundle branch block or left ventricular hypertrophy and were not considered diagnostic of infarction. The tall, sharply peaked T wave in Lead V_2 was somewhat suggestive of hyperpotassemia, which may have been present, in view of the fact that the blood urea reached 272 mg. per cent. Unfortunately, no subsequent electrocardiograms were obtained for comparative purposes during the last four days of his life.

Pathologic Findings.—The heart weighed 360 grams and exhibited a dense infarct, involving the subendocardial half of the anteroseptal wall, extending through the left side of the septum to the subendocardial one-third of the posteroseptal wall, as outlined in Fig. 12. The infarct was recent in origin, but was believed to have been present at the time the electrocardiogram was made and was presumably responsible for the epigastric pain at the onset of his present illness, since no other cause was found. The paucity of diagnostic electrocardiographic signs is noteworthy. Q waves would have been expected in Leads V_3 and V_4, in view of the dense infarct of the subendocardial half of the anteroseptal wall, but not in Leads V_5 and V_6, since the infarct did not extend appreciably into the lateral wall. A Q wave would also have been expected in Lead aV_F, which reflected the potential variations of the subendocardially infarcted posterior wall of the left ventricle. The presence of an initial R wave in Leads V_3, V_4, and aV_F was due most likely to reversal in septal activation to a direction from right to left. This might have resulted from coexistent left bundle branch block or from infarction of the Purkinje network in the left side of the septum. The latter alternative was favored because it corresponded better with the location of the infarct at autopsy. The absence of diagnostic changes in the RS-T segment and T wave may have been due to preservation of the subepicardial half of the anteroseptal wall. Pulmonary emphysema, associated with anthracosis, may have been a factor in the low voltage in the axillary and limb leads.

Case 82.—A 78-year-old man was admitted in coma with hemiplegia due to cerebral hemorrhage. He was known to have had hypertension, but no further history was obtainable. He died on the sixth hospital day of the cerebrovascular accident.

Electrocardiographic Findings.—An electrocardiogram obtained on the fifth hospital day, after the administration of 0.4 Gm. of digitalis, is reproduced in Fig. 10, *D*. On the basis of a QRS duration of 0.12 second, an initial upright deflection in Leads V_5, V_6, and aV_L, and notching or slurring of the R wave in these leads, a diagnosis of left bundle branch block was made. In Leads V_1 through V_3 there was a minute initial R wave followed by a deep, broad, slurred S wave typical of the findings obtained through precordial leads over the right ventricle in cases of left bundle branch block. From a quick perusal of Lead V_4, the QRS complex would appear to consist of a deep, slurred Q wave and a small late R wave, fairly typical of the findings produced in this lead by infarction of the anteroseptal aspect of the apex. This was the interpretation placed upon Lead V_4 in the ante-mortem study of the tracing; however, the QRS duration in Lead V_4, as measured from the beginning of the major downstroke to the end of the descending limb of the R, was only 0.08 second, as compared with 0.12 second in other leads. More careful scrutiny revealed a small, slurred initial R wave 0.04 second in duration, which preceded the major downstroke. Thus, Lead V_4 actually showed an RSR′ complex, transitional in type between the right ventricular pattern recorded in Lead V_3 and the left ventricular in Lead V_5. All cycles of Lead aV_F showed a broad, slurred QS complex, which, in the ante-mortem interpretation, was taken as evidence of coexistent posterior infarction. In view of the fact that the potential variations of the posterobasal aspect of the left ventricle were transmitted to both upper extremities to cause a comparable broad, slurred R wave in both Leads aV_R and aV_L, it was more plausible to assume that the right ventricle rested on the diaphragm and that the broad, slurred QS complex of Lead aV_F was representative of the findings often obtained over the normal right ventricle in cases of left bundle branch block. The standard leads also showed left bundle branch block with a QS complex in Leads II and III, which, like that in Lead aV_F, had two possible explanations.

Pathologic Findings.—The heart weighed 580 grams and showed three separate healed infarcts, as outlined in Fig. 13. A transmural infarct of the basal half of the posterior aspect of the left ventricle had caused considerable thinning of the wall. A second infarct involved the left side of the septum and the subendocardial half of the anterior and lateral walls in the second and third segments and the entire septal and anterolateral walls in the apical segment. A third small subendocardial anterolateral infarct in the fourth and fifth segments may have represented an upward extension of the apical infarct. Microscopic sections of all three infarcts showed dense fibrosis with residual islands of intact muscle. Although autopsy revealed both the anterior and posterior infarcts predicted in the ante-mortem interpretation of the electrocardiogram, there is considerable doubt, from a restudy of the tracing, that either diagnosis was justified. An RSR′

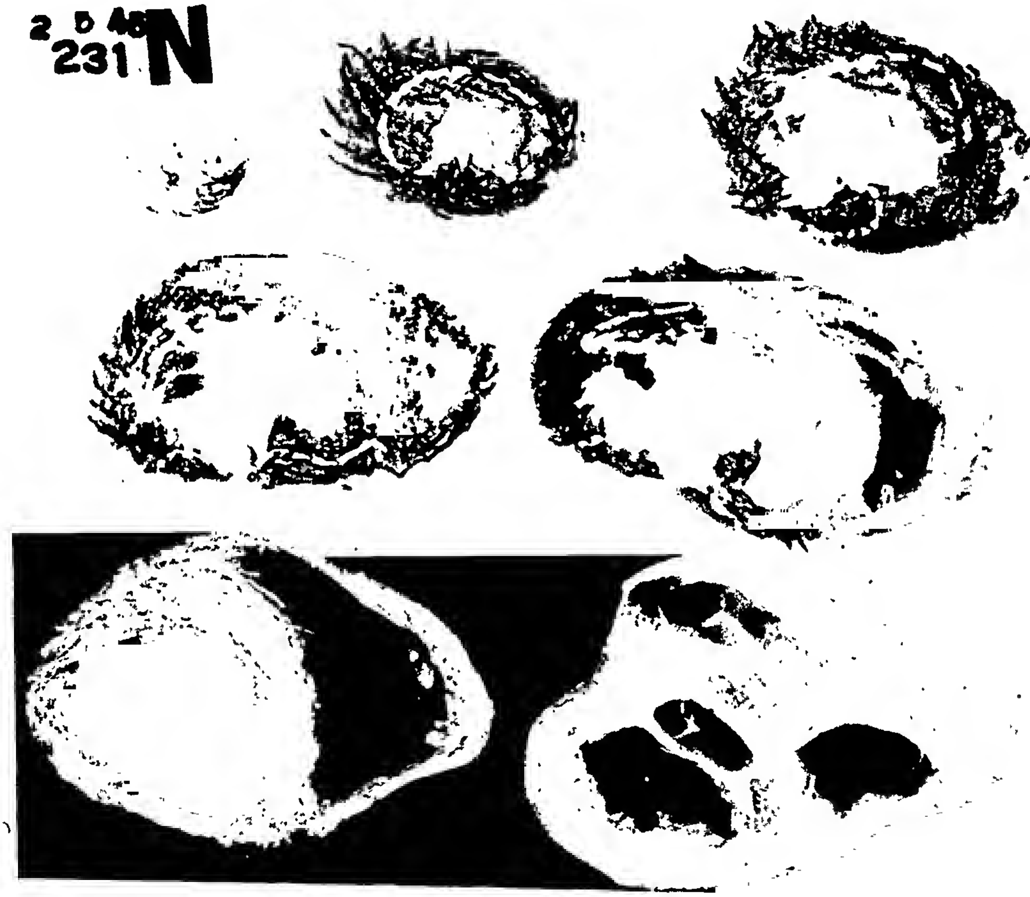

Fig. 13.—Roentgenogram of the injected heart in Case 82, showing position of old, healed anterolateral, septal, and posterior infarcts.

complex like that of Lead V_4 may occur at the transitional zone in left bundle branch block, uncomplicated by infarction, as will be emphasized in a subsequent communication. In the presence of left bundle branch block, it is difficult or impossible to make a diagnosis of old anterior infarction, since the potential of the left ventricular cavity is initially positive, thus causing a preliminary upright deflection in all semidirect leads over the left ventricle. The question remains as to whether the QS complex in Leads aV_F, III, and II was due to the posterobasal infarct found at autopsy or merely to the horizontal position of the heart with reference of the potential variations of the right ventricle to the left leg. In spite of the apparent correlation with the posterior infarct, it seems more likely that the QS complex was of right ventricular origin and that the

finding of the posterior infarct was merely fortuitous. Although the left side of the apical half of the septum was involved in the anterior infarct, the left bundle branch block was probably independent and due to an unrecognized lesion higher in the septum.

CASE 83.—A 56-year-old man was admitted to the hospital in a critical state with lobar pneumonia due to Friedländer's bacillus, complicated by fibrinous pericarditis. Past history was unobtainable. Death occurred from a pulmonary abscess twelve days after admission. No cardiac glycosides were given.

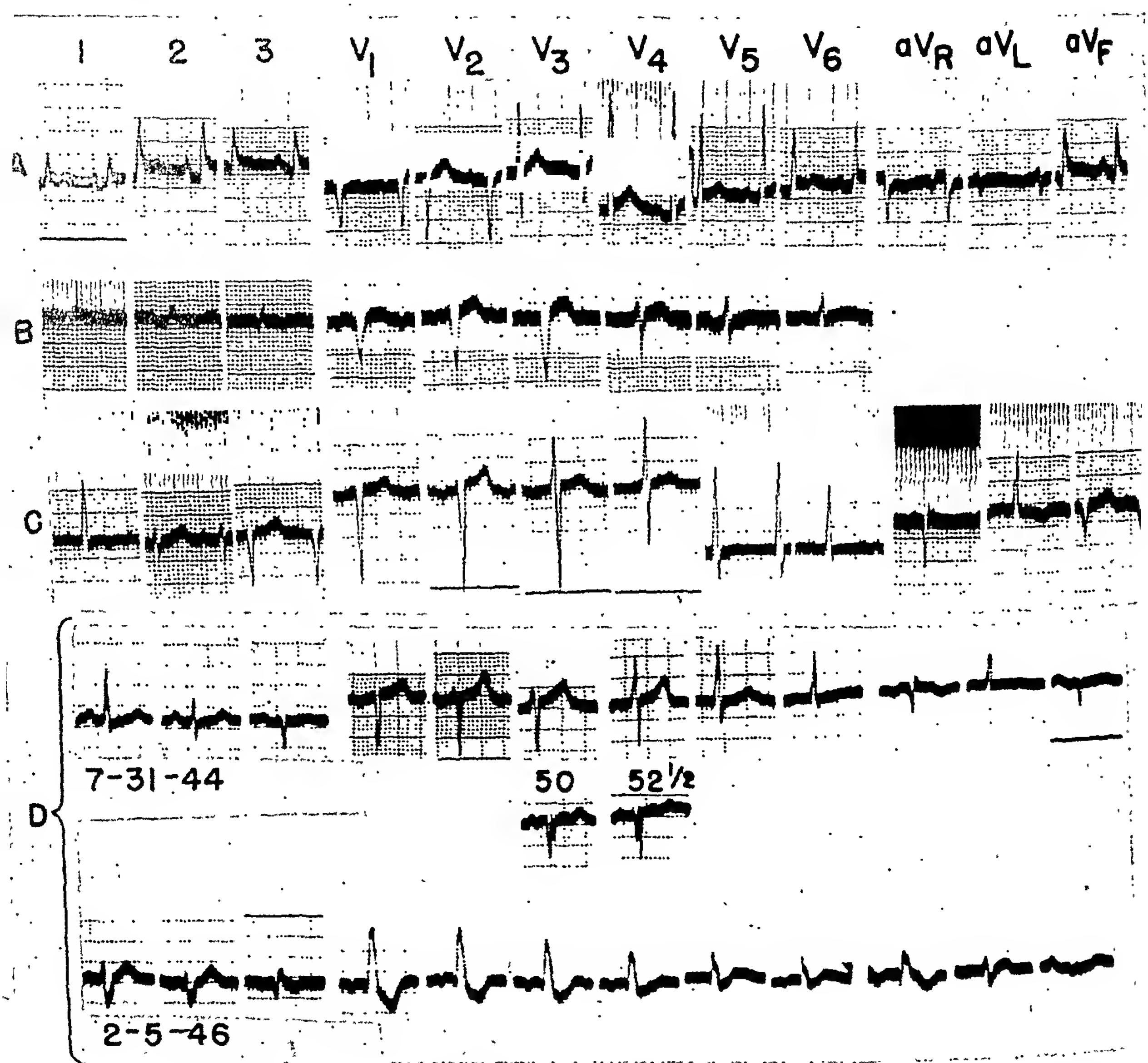

Fig. 14.—Healed primary septal infarction. *A*, Case 83; *B*, Case 84; *C*, Case 85; *D*, Case 86.

Electrocardiographic Findings.—Electrocardiograms obtained on the fifth and ninth hospital days were essentially the same, the former being reproduced in Fig. 14, *A*. The most striking finding was the elevation of the RS-T segment in Leads V_4 through V_6 and aV_F, the latter carrying over into Leads II and III. In view of the tall R wave without antecedent Q wave in Leads V_4 through V_6 and the upward concavity of the RS-T segments, the displacement in these leads was attributed to acute pericarditis. A Q wave was present in Lead aV_F, but was only 0.02 second in

duration and 15 per cent of the amplitude of the succeeding R wave. For this reason and because of the particularly characteristic contour of the RST-T complex in Lead aV_F, the findings in this lead were also attributed to pericarditis. Leads V_{3R} and V_1 displayed a QS complex, which was notched near its onset, and Lead V_2, which also reflected the potential variations of the right ventricle and right side of the septum, exhibited a Q wave of 1.0 mm., an R wave of 1.0 to 3.0 mm., and an S wave of 8.0 to 13.0 millimeters. Although a smooth QS deflection may occur as a normal variant in these leads, a Q wave followed by a small R wave or R-wave equivalent (notch) and then by a deep S wave is abnormal and is representative of infarction of the septum. The septal infarct was considered healed because of the absence of T-wave abnormalities in Leads V_{3R}, V_1, and V_2. The standard leads were diagnostic of pericarditis, but revealed no evidence of septal infarction.

Fig. 15.—Roentgenogram of the injected heart in Case 83, showing position of old, healed primary septal infarct.

Pathologic Findings.—The heart weighed 526 grams and showed a universal acute fibrinous pericarditis and a 400 c.c. effusion. A well-vascularized, healed, patchy infarct was found in the apical half of the septum, extending for a short distance into the anteroseptal wall of the left ventricle, as shown in Fig. 15. The failure of the posterolateral portion of the left ventricle to inject was due to a technical error, since sections revealed no evidence of infarction in this region. It is noteworthy that the infarction was limited to the apical half of the septum, whereas the electrocardiographic signs were confined to Leads V_{3R}, V_1, and V_2. This discrepancy was attributable to the position of the transitional zone between Leads V_2 and V_3 and, hence, to the fact that Leads V_{3R}, V_1, and V_2 were the only leads reflecting the potential variations of the right ventricle and right side of the septum. The R wave or notch in these leads was presumably produced by activation of the outer wall of the right ventricle, and the antecedent Q wave could

be correlated with the septal infarction found at autopsy and was probably a manifestation of reversal in the direction of septal activation. The continuation of the septal infarct for a short distance into the subendocardial portion of the anterior wall of the left ventricle was not evident electrocardiographically. The slight extension into the posteroseptal wall was probably not a factor in the production of the normal Q wave recorded in Lead aV_F.

CASE 84.—A 54-year-old diabetic man noted his first cardiovascular symptoms three months before hospital admission, when he had an attack of prolonged constrictive retrosternal pain and dyspnea which required morphine. Since then he had several transient attacks, generally relieved by nitrites. He was admitted in left ventricular failure two hours after the onset of a more severe retrosternal pain, which had failed to respond to nitrites. Death occurred on the fifth hospital day.

Electrocardiographic Findings.—An electrocardiogram obtained seven hours before death and after the administration of 1.8 mg. of Cedilanid on the three preceding days is reproduced in Fig. 14, *B*. The QRS complexes in both the precordial and extremity leads showed no essential difference from those in three preceding tracings. Although a first glance raised the question of a conduction defect, the measurement of the QRS complex did not exceed 0.10 second and the slurring in the extremity leads was of the type customarily found in the presence of low voltage. The QR complex and inverted T wave of Lead aV_F were strongly suggestive of posterior infarction, but because of a borderline ratio and low voltage, an unequivocal diagnosis was not justified. A slurred QS complex was found consistently in Leads V_{3R}, V_1, V_2, and V_3. An initial upright deflection was present constantly in Leads V_4 through V_7. The R wave was low in voltage in these leads, but increased progressively at the expense of the S wave as the electrode was moved from Position V_4 toward the left. The question arose as to whether the absence of the R wave in Leads V_1 through V_3 was due to infarction of the septum or whether it was a variant sometimes encountered in precordial leads over the right ventricle in cases of left ventricular hypertrophy. If a posterior infarct had been present, as suggested by the findings in Lead aV_F, an accentuation of the R-wave would have been expected in precordial leads. Thus, an infarction of the septum, which obliterated the positive potentials ordinarily referred to the right side of the precordium during septal activation, seemed the more plausible explanation for the QS pattern in leads from the right side of the precordium. Since an initial R wave was present in Lead V_4 and all leads farther to the left, there was no electrocardiographic evidence of infarction of the anterolateral wall of the apex.

Pathologic Findings.—The heart weighed 310 grams and exhibited a large infarct which extended in patchy fashion through the entire length of the septum and continued backward into the subendocardial half of the posteroseptal wall in all segments and into the subendocardial half of the anteroseptal wall in the apical fourth of the left ventricle. Thus, the position of the infarct was like that in Case 75, shown in Fig. 7, with the following exceptions: the septal lesion was present in the apical segment and extended into the anteroseptal wall of this segment in the same fashion as in the second segment of Fig. 7 and also extended into the entire length of the posteroseptal wall in the same fashion as in the basal half of Fig. 7. The bulk of the infarct was judged to be of more than one month's duration, but patchy areas of recent reinfarction were discernible microscopically. Although the septal involvement in this case was more extensive than in some of the cases of right bundle branch block, the QRS interval was within normal limits. The absence of the initial R wave in Leads V_{3R}, V_1, V_2, and V_3 was probably a manifestation of the septal infarction, and the QR pattern in Lead aV_F was apparently a result of the posterior infarct. The extension of the infarct into the anteroseptal aspect of the apex may have been a factor in the QS complex recorded in Lead V_3 and should have resulted in an abnormal Q wave in Lead V_4, as well. The absence of infarction of the lateral wall of the apex was in keeping with the initial R wave in Leads V_5 through V_7.

CASE 85.—A 79-year-old woman was admitted to the hospital in coma with right hemiplegia due to cerebral hemorrhage. She was known to have had hypertension, but no further past history was obtainable. Death occurred on the ninth hospital day from the cerebral vascular accident. No cardiac glycosides were given.

Electrocardiographic Findings.—An electrocardiogram obtained on the second hospital day is reproduced in Fig. 14, *C.* The QRS interval was 0.08 second, the initial deflection was upright in all precordial leads, and the R wave showed the normal increase in amplitude and duration as the electrode was moved from Position V_1 to V_5. The inversion of the T wave in Lead aV_L, together with the flattening in Leads V_5 and V_6, raised the question of left ventricular hypertrophy, but an unequivocal diagnosis could not be made, since the time interval from the beginning to the peak of the R wave in these leads was within normal limits. All cycles of Lead aV_F showed a QS complex with a slurred descending limb, requiring 0.04 second from onset to nadir. The question arose as to whether this QS complex was a manifestation of an old healed infarct of the posterior wall of the left ventricle or was due to transmission of the potential variations of the right ventricle to the left leg, as a result of horizontal position of the heart. Although a positive differentiation could not be made, the former alternative was favored in the ante-mortem interpretation of the tracing. Repetition of Lead aV_F in different postures, as well as esophageal leads, would have been helpful in reaching a definite decision.

Pathologic Findings.—The heart weighed 390 grams and showed moderate concentric left ventricular hypertrophy. There was an old, completely healed, patchy infarct of the interventricular septum, almost identical in position, size, and shape to that in Case 83, Fig. 15. The relatively small initial R wave of Leads V_1 and V_2 may have been derived from islands of uninfarcted muscle in the septum or from the outer wall of the right ventricle. Although the infarct extended into the posterior aspect of the apical two segments in a manner almost identical with that of Fig. 15, it is doubtful that this limited area of involvement could have accounted for the QS complex of Lead aV_F. The other alternative of horizontal position with transmission of potential variations of the right side of the septum and right ventricle to the left leg seemed the more likely explanation for the QS complex recorded in Lead aV_F. In view of the slurring and prolongation of its descending limb, this QS complex was probably a manifestation of the septal infarct.

CASE 86.—A 74-year-old man with diabetes mellitus and hypertension was first admitted to the hospital on July 26, 1944, in congestive failure. During the remaining twenty months of his life, he was troubled with exertional dyspnea and recurrent cardiac failure, for which he had been hospitalized elsewhere. No definite history of angina pectoris or myocardial infarction was elicited. He was readmitted in cardiac decompensation in April, 1946, and had an uneventful course until the ninth hospital day, when he suddenly died.

Electrocardiographic Findings.—Electrocardiograms taken on July 29, 1944, before the administration of digitalis, and on Feb. 5, 1946, while the patient was on maintenance doses, are reproduced in Fig. 14, *D.* The tracings taken during the first admission showed a small, brief initial R wave and a prominent S wave in right ventricular Leads V_1 through V_3, and a minute Q wave, prominent R wave, and late intrinsicoid deflection (0.06 second after onset of the QRS complex) in left ventricular Leads V_5, V_6, and aV_L. These findings were attributed to left ventricular hypertrophy. Lead aV_F exhibited a QS complex, strongly suggestive of posterior infarction, but not diagnostic because of its brief duration and low voltage. In standard Lead III there was a small, slurred initial R wave which was evidently derived from the initial negativity of the left arm. Thus, the standard leads showed no evidence of posterior infarction. For further evidence, esophageal leads were obtained. Judging from the contour of the P wave in Leads E_{50}, E_{52}, and E_{55}, the electrode was behind the ventricle and a short distance below the auriculoventricular groove. The W-shaped QRS complex registered in these leads was regarded as diagnostic of posterior infarction and thus confirmatory of the findings in Lead aV_F. From the contour of the T wave, the posterior infarct was considered to be old and healed. In the tracing of Feb. 5, 1946, there was a striking change in the first four precordial leads, characterized by the appearance of a tall R wave and late intrinsicoid deflection, together with RS-T depression and T-wave inversion, indicative of right bundle branch block. Because of the presence of a distinct Q wave in these leads, the right bundle branch block was attributed to infarction of the septum. The electrode at Positions V_3 and V_4 was believed to be over the right side of the heart, not only because of the similarity of the QRS pattern to that in Leads V_1 and V_2, but also because of the

inversion of the sinus P waves in all four leads. The diphasic P waves in Leads V_5 and V_6 and the shift in the slurring to the descending limb of the R wave suggested that these leads were at the transitional zone. Thus, the Q wave in all six precordial leads could have been a manifestation of an infarct limited to the septum. Lead aV_L displayed an initial R wave, a broad, slurred S wave, and upright T wave, which is representative of the pattern registered in precordial leads over the left ventricle in cases of right bundle branch block. The initial downward deflection in Leads aV_F, II, and III was considered a remnant of the old posterior infarct. Thus, the old posterior infarct was recognizable in Lead aV_F and a subsequent infarct of the septum in precordial leads. The changes in the RS-T segments and T waves were attributed to superimposed digitalis effect. In a final tracing, taken one week before death, the QRS pattern in leads from the right side of the precordium showed no essential change, but the transitional zone had shifted sufficiently to the right so that Leads V_5 and V_6 exhibited an initial R wave, a slightly delayed intrinsicoid deflection, and a subsequent broad, slurred S wave, typical of the findings in left ventricular leads in left ventricular hypertrophy, complicated by right bundle branch block.

Fig. 16.—Roentgenogram of the injected heart in Case 86.

Pathologic Findings.—The heart weighed 753 grams and exhibited an old healed infarct, which was confined to the subendocardial half of the posterior wall in the fourth and fifth segments and extended from the posterior wall through the interventricular septum into the subendocardial portion of the anteroseptal region in the apical three segments, as outlined in Fig. 16. The infarct was well fibrosed throughout and appeared confluent from the posterior wall into the septum. Despite the lack of pathologic demarcation, it is probable, from the serial electrocardiograms, that the posterior portion was present in July, 1944, and accounted for the changes in Lead aV_F and

the esophageal leads, and that the septal portion developed some time during the next one and one-half years and produced right bundle branch block. The distribution of the septal infarct at autopsy was in keeping with the interpretation of the tracing of Feb. 5, 1946.

COMMENT

Classification of Pathologic Findings Referable to Septal Infarction.—The material to be summarized comprises eighty-nine cases in which infarction was demonstrated at autopsy in one-third or more of the interventricular septum. The series was classifiable pathologically into three main groups: Group A, primary septal infarction, six cases; Group B, septal involvement associated with extensive anterior or anteroposterior infarction, fifty-nine cases; Group C, septal continuation of posterior infarction, twenty-four cases.

In Group A, the lesion classed as a primary septal infarction was distributed in patchy fashion through the entire septum in one patient (Case 84), through the basal four-fifths in one patient (Case 75), and was limited to the apical half in three patients (Cases 83, 85, and 86), and to the middle half in one patient (Case 76). It continued subendocardially for a very short distance into the anteroseptal and posteroseptal walls in all patients and was confluent with an independent posterior infarct of different age in two patients (Cases 75 and 86). Electrocardiographic studies were made during the acute stage of the septal lesion in two patients (Cases 75 and 76) and only after healing in the other four patients.

The major portion of the lesion in the fifty-nine cases of Group B was located in the free anterior and anterolateral walls of the left ventricle, but the infarct continued into the apical one-third or more of the septum, often reaching the free posterior wall. The series was divisible into three subgroups, in accordance with the extent of the septal portion of the lesion: (1) Infarction confined to the apical third. This distribution was found in six patients (Cases 22, 42, 43, 64, 67, and 96). The lesion was further limited to the left side of the septum in five of the foregoing patients, but was transseptal in one (Case 22). The infarct was recent in Case 22 and healed in the remainder. (2) Infarction occupying the apical one-half to two-thirds of the septum. This distribution was found in thirty-one patients (Cases 29 through 33, 37, 41, 46, 47, 48, 50 through 58, 61, 62, 63, 65, 66, 69, 73, 77, 79, 81, 82, and 91). The lesion was confined to the left side of the septum in twelve of the foregoing patients and to the anterior half in three. In the other sixteen patients, the lesion in the apical third or more of the septum extended from one endocardial surface to the other and from the anterior to the posterior terminus, but near its upper boundary the infarct usually tapered off to occupy the left side of the anterior portion of the septum. The infarct within these boundaries was not necessarily complete and often was patchy in distribution. Electrocardiographic studies were made during the acute stage in seventeen patients and after healing in the other fourteen. (3) Infarction involving more than the apical two-thirds of the septum. This distribution was found in twenty-two patients (Cases 23 through 27, 34, 35, 36, 38, 39, 40, 49, 59, 70, 71, 72, 74, 78, 80, 151, 152, and 153). The infarct was confined to the left side of the septum in four of the

foregoing patients and to the anterior half in two. In the remainder, the lesion was transseptal in the apical half or more, but tended to narrow to the left side of the anterior portion in the basal one-half to one-third of the septum. The infarct was recent in eighteen patients and healed in four.

The infarct in the twenty-four cases of Group C involved the posterior wall of the left ventricle primarily and continued into the posterior portion of the septum. The cases were classifiable into three subgroups, according to the location and extent of the septal lesion: (1) Infarction of the apical one-third to two-thirds of the septum. This distribution was present in six patients (Cases 99 through 102, 111, and 114). The lesion represented an extension of a posteroapical infarct and was confined to the posterior one-third to one-half of the septum in four patients and to the left side in two. (2) Infarction of the basal one-third to two-thirds of the septum. This distribution was present in twelve patients (Cases 87, 89, 90, 92, 103, 108, 121, 125, 126, 127, 128, and 136). The lesion was confined to the posterior one-third to one-half of the septum in all patients and to the left side, as well, in seven. (3) Infarction extending the entire length of the septum. This distribution was present in six patients (Cases 60, 88, 95, 104, 110, and 124). The lesion was limited to the posterior one-third to one-half of the septum in all patients and to the left side in three.

Classification of Electrocardiographic Findings Associated With Septal Infarction and Correlation With Pathologic Findings.—The electrocardiographic patterns encountered in the series of eighty-nine cases were classifiable into one or more of the following categories: (1) auriculoventricular block; (2) right ventricular conduction defects; (3) left ventricular conduction defects; (4) Q waves and/or RS-T segment displacement in right ventricular leads directly referable to, or at least suggestive of, septal infarction; (5) absence of direct evidence of a septal lesion.

The QRS interval was 0.12 second or more in the thirty cases classified primarily into combined Classifications 2 and 3, whereas the measurement was less than 0.12 second in the remaining fifty-nine cases falling into combined Classifications 4, 5, and 6. The expected trend toward larger septal infarcts in cases with prolonged QRS interval than in cases with normal QRS interval was not borne out at autopsy. The lack of significant difference in the size of the septal infarcts in the two groups may have been due to the fact that the prolongation of the QRS complex in the majority of the thirty cases was believed to have been independent of the septal infarct. Further consideration of electrocardiographic-pathologic correlations will be deferred to the discussion of each individual group.

1. *Auriculoventricular Block*: Complete A-V block was found in four patients (Cases 25, 88, 96, and 104). It was associated with auricular tachycardia in Cases 96 and 25 and was undoubtedly independent of the infarct confined to the apical one-third of the septum in the former and may have been unrelated to the massive septal extension of an anterior infarct in the latter. Complete A-V block was associated with a sinus tachycardia, averaging 140 beats per minute, in Case 88 and with auricular fibrillation in Case 104, but was

believed referable to an extension of a large recent posterior infarct into the base of the septum in both cases. A transient A-V nodal tachycardia with a 2:1 ratio and a terminal auricular flutter with similar ratio were found in Case 87, but sinus rhythm with a normal P-R interval was also observed in this case, despite the fact that the posterior half of the base of the septum exhibited transmural infarction, complicated by a 3.0 cm. perforation. Twelve other cases were observed with sinus rhythm during life and infarction of the posterobasal portion of the interventricular septum at autopsy and it is noteworthy that the P-R interval was 0.20 second or less in each case.

2. *Right Ventricular Conduction Defects*: Defects of this type were found in a total of fourteen patients, including three with primary septal infarction (Cases 75, 76, and 86), nine with primary anterior infarction (Cases 54, 69 through 74, 78, and 153), and two with primary posterior infarction (Cases 87 and 110). The conduction defect was established in all cases by the demonstration of a QRS interval of 0.12 second or longer in complexes derived from impulses of supraventricular origin and was localized to the right ventricle by the presence of a prominent late R wave in leads over the right side of the heart, together with an abnormally delayed intrinsicoid deflection, commencing 0.08 second or more after the onset of the QRS complex.

The QRS-T pattern in the precordial leads of one patient (Case 110) was similar to that of uncomplicated right bundle branch block, and the conduction defect in this case was probably independent of the patchy infarct of the left side of the posterior third of the septum found at autopsy. One other patient (Case 153) displayed a transient right bundle branch block manifested by an exceptionally tall initial R wave and a markedly depressed RS-T junction in Leads V_1 and V_2 and by a small Q wave and a tall late R wave in right ventricular Lead V_3. The findings in the first two precordial leads were more in keeping with the transient right bundle branch block which sometimes accompanies acute left ventricular failure, but the findings in Lead V_3 were strongly suggestive of the acute septal infarction found at autopsy.

Following the established custom, the term "right bundle branch block" was used to characterize the conduction defect in the individual reports of the other twelve cases. In the strict sense, this terminology was incorrect since (1) the QRS-T abnormalities were directly referable to a septal lesion, but differed significantly from the pattern in uncomplicated right bundle branch block; (2) the infarction in some of the cases involved the apical portion of the septum and spared the anatomical site of the right bundle branch.

The QRS-T pattern in right ventricular leads of these twelve cases exhibited distinctive features which differed from the pattern of uncomplicated right bundle branch block in one or both of the following respects: (a) the direction of the initial phase of the QRS, (b) the position of the RS-T junction. The initial upstroke characteristically recorded in right ventricular leads in uncomplicated right bundle branch block represents positive potentials derived from septal activation and transmitted to the right ventricular cavity and right precordium. The replacement of this initial R wave by an abnormal Q wave occurs as a manifestation of the conduction defect associated with sep-

tal infarction when negative potentials transmitted from the left ventricular cavity through the infarcted septum to the right precordium exceed positive potentials coming from activation of intact remnants of the septum. A distinct Q wave, a late R wave, and an abnormally delayed intrinsicoid deflection were demonstrated in right ventricular leads of ten patients (Cases 69, 70, 72, through 76, 78, 86, and 87) and were considered diagnostic of septal infarction in all cases, with the possible exception of Case 87. The right ventricular conduction defect developed terminally in this patient in association with auricular flutter and a ventricular rate of 176. The possibility of obliteration of the customary initial R wave from Lead V_1 by the flutter wave was deemed unlikely, but could not be excluded positively. A minute initial R wave was present in right ventricular Leads V_1 through V_3 in Cases 54 and 71, but the conduction defect was ascribed to acute septal infarction because of the presence of classical upward displacement of the RS-T segment. Whereas uncomplicated right bundle branch block usually causes depression of the RS-T junction in leads from the right precordium, the right ventricular conduction defect associated with acute septal infarction was manifested by an elevated or at least an isoelectric RS-T junction in these leads in eleven of the cases.

The septal portion of the infarct at autopsy was limited to the apical half of the septum in two patients (Cases 73 and 86), to the middle half in one (Case 76), to the apical two-thirds in two patients (Cases 54 and 69), and thus failed to reach the anatomic site of the right branch of the bundle of His. The position of the lesion in these five cases suggested that the late arrival of the impulse at the epicardial surface of the free wall of the right ventricle was due to interruption of conduction through the Purkinje network beneath the endocardium of the right side of the septum rather than through the right branch of the bundle of His. If this premise be correct, the conduction defect in these cases was not a right bundle branch block in the strict sense of the term. On the other hand, the septal portion of the infarct in Case 87 was confined to the posterior half of the basal part of the septum. If this lesion was responsible for the terminally developing delay in arrival of the impulse at the epicardial surface of the right ventricle, its anatomic position suggested that it acted by interruption of conduction through the right bundle branch. The infarct in the other six cases involved more than the apical two-thirds of the septum and may have caused delay in the arrival of the impulse at the epicardial surface of the right ventricle, either by involvement of the right bundle branch or by destruction of the Purkinje network beneath the endocardium of the right side of the septum. Since the abnormal Q wave, the tall R wave, and the late intrinsicoid deflection due to septal infarction that has involved the right branch of the His bundle constitute a pattern which is indistinguishable from that due to infarction that has spared this portion of the septum, we shall continue to employ the customary term, right bundle branch block due to septal infarction, to designate this pattern.

The small but definite initial R wave in Leads V_1 through V_3 in Case 54 and the probable small initial R wave in the same leads in Case 71 require further discussion. Autopsy disclosed a recent transmural infarct, involving the

apical half of the anterior wall and septum and the apical one-third of the lateral and posterior walls in the former case, and a recent transmural infarct in the latter case, which was similar in distribution, but approximately one and one-half times as large. The right bundle branch block and RS-T segment displacement in Leads V_1 through V_3 were attributable to the septal infarct and the atypical initial R wave could be explained when consideration was given to the factors governing the direction of the first phase of the QRS complex under these circumstances. Whether or not a Q or R wave is recorded depends upon (1) the relative size of the preserved and infarcted portions of the septum, and (2) the magnitude of the opposing negative potentials developing in the left ventricular cavity during activation of residual living septal muscle. The initial negativity of the left ventricular cavity is normally due to the early arrival of the impulse and early onset of activation of the left side of the septum and anteroseptal wall of the left ventricle. When a portion of the septum is infarcted, these initial negative potentials are transmitted through the infarct to the right ventricular cavity to oppose the positive potentials simultaneously developing therein as a result of activation of preserved remnants of the septum. Infarction of most of the anterior wall and septum in both cases probably postponed the development of significant negativity in the left ventricular cavity for a brief interval, during which weak positive potentials referred to the right ventricular cavity from activation of the intact posterobasal portion of the septum were recorded as a small R wave. This was replaced by a deep downstroke as soon as the impulse reached and began to activate the uninfarcted basal portions of the posterior and lateral walls of the left ventricle.

After the establishment of the diagnosis of right bundle branch block due to septal infarction, further study of the electrocardiogram is indicated for evidence of extension of the lesion into the free anterior and posterior walls of the left ventricle. The recognition of associated infarction of the anterior wall depends upon identification of the transitional zone and examination of thoracic leads farther to the left. The detection of extension into the posterior wall is even more difficult, depending upon the interpretation of Lead aV_F in the light of the findings in the precordial leads.

The decision as to the presence or absence of associated infarction of the anterior wall of the left ventricle is not difficult when the transitional zone is situated somewhere between precordial Positions 1 and 4, since the customary precordial leads then afford adequate exploration of the anterolateral wall of the left ventricle. This is illustrated by an analysis of the findings in Cases 76 and 75, in contrast to those in Cases 69 and 74. The transitional zone in Case 76 was located at precordial Position 2 because of the registration of a small quadriphasic QRS in Lead V_2. Leads V_3 through V_6 reflected the potential variations of the left ventricle and displayed a small initial R wave and a broad S wave typical of the findings over the normal left ventricle in right bundle branch block, from which it was concluded that the septal infarct did not extend significantly into the anterior wall of the left ventricle. The transitional zone in Case 75 was broader, covering both the V_2 and V_3 positions, as evidenced by a QRS-T pattern in Leads V_2 and V_3, which was intermediate between that in

right ventricular Lead V_1 and left ventricular Leads V_4 through V_6. The absence of Q waves from the last three precordial leads indicated that the septal infarct in Case 75 did not extend significantly into the anterior wall of the left ventricle. These conclusions were confirmed at autopsy in both cases. The QRS-T pattern in Lead V_1 in Cases 74 and 69 (tracing of December 1) was closely comparable with that in Lead V_1 in Cases 76 and 75, and the transitional zones were located at Position V_2, as evidenced by a less delayed intrinsicoid deflection and a succeeding S wave in Lead V_2. The abnormal Q waves and elevation of the RS-T segment in left ventricular Leads V_4 and V_5 in Cases 74 and 69 contrasted sharply with the findings in corresponding leads in the two previous cases and indicated that the septal infarct continued into the anterior and anterolateral walls of the left ventricle. This conclusion was confirmed at necropsy in both cases.

The transitional zone usually is located well to the right of the midclavicular line in uncomplicated right bundle branch block, but is not infrequently displaced to the left of this position in right bundle branch block due to septal infarction. Diagnostic difficulties arise under these circumstances, due to the fact that Leads V_3; V_4, and perhaps even V_5 reflect principally the potential variations of the right side of the septum and right ventricle rather than the left side of the septum and left ventricle. The abnormal Q wave, late R wave, and delayed intrinsiocoid deflection in Leads V_3 through V_5 of Case 86 was not due to infarction of the anterior wall of the left ventricle, but rather to septal infarction with right bundle branch block and displacement of the transitional zone to the left, as shown by the similarity in shape of the QRS complex and time of onset of intrinsicoid deflection to that in Lead V_1 and also supported by the finding of inverted sinus P waves in Leads V_1 through V_4, indicating proximity of the electrode to the right atrium. The absence of significant extension into the anterolateral wall of the left ventricle of this patient was suggested by the normal initial R wave in left ventricular Leads V_6 and aV_L. This was confirmed at necropsy.

Displacement of the transitional zone into the axilla may conceal signs of infarction of the free anterior wall of the left ventricle. For example, the abnormal Q wave and tall late R wave in the first five precordial leads in Case 72 were chiefly representative of the potential variations of the epicardial surface of the right ventricle, as shown by the synchronism of the intrinsicoid deflections. Since Lead V_6 revealed a small quadriphrasic QRS complex typical of the transitional zone and Lead aV_L revealed a QR pattern of right ventricular origin, resembling that in Lead V_2, the customary precordial leads did not provide adequate exploration of the anterolateral wall of the left ventricle and additional leads would have been required to make the diagnosis of the associated infarction of the anterolateral wall of the left ventricle found at autopsy. The QR complex in Leads V_4 and V_5 in Case 73 differed in contour from that in Leads V_1 through V_3, but the simultaneous onset of the intrinsicoid deflection in these five leads indicated that the findings in Leads V_4 and V_5 were referable to infarction of the septum rather than the anterior wall of the left ventricle. Because of the frequency of leftward displacement of the transitional zone in

association with right bundle branch block due to septal infarction, additional leads, particularly V_7 and V_8, should be obtained.

Errors in the interpretation of the findings in Leads aV_L and aV_F are especially prone to occur in cases of right bundle branch block due to septal infarction, unless due cognizance is taken of cardiac position. Septal infarction may be manifested by an abnormal Q wave and a late R wave in Lead aV_L when the heart is in the vertical position, due to predominant transmission of the potential variations of the right side of the septum and epicardial surface of the right ventricle to the left arm. Thus, the initial Q wave and late R wave in Lead aV_L in Case 72 were referable to septal rather than lateral infarction, as shown by the correspondence in the contour of the QRS complex and time of onset of the intrinsicoid deflection with that in right ventricular Lead V_2. Vertical position was confirmed in this case by the registration of a relatively narrow R wave and broad S wave in Lead aV_F, typical of the findings obtained over the left ventricle in the presence of right bundle branch block. Septal infarction may be manifested by a small notched or W-shaped QS complex in Lead aV_L when the heart is in semivertical position, due to predominant transmission of the potential variations of the transitional zone at the junction of septum and anterior wall to the left arm. This interpretation of the notched QS complex recorded in Lead aV_L of Case 75 was borne out by autopsy, which revealed infarction of the septum, but not of the lateral wall of the left ventricle.

Septal infarction may be manifested by an abnormal Q wave and a late R wave in Lead aV_F, when the heart is in a horizontal position, due to predominant transmission of the potential variations of the right side of the septum and epicardial surface of the right ventricle to the left leg. Thus, the abnormal QR pattern in Lead aV_F (and also in Leads II and III) of Case 74 was referable to septal rather than posterior infarction, as shown by the correspondence in contour of the QRS complex and time of onset of the intrinsicoid deflection with that in right ventricular Lead V_1. Horizontal cardiac position was verified in this case by the registration of a relatively narrow R wave and a broad S wave in Lead aV_L, typical of the findings obtained over the left ventricle in the presence of right bundle branch block. On the other hand, a diagnosis of septal infarction, extending into the posterior wall of the left ventricle, could be made in Case 69 from the registration of an abnormal QR pattern in Leads aV_F, III, and II, which differed significantly from the abnormal QR pattern of septal origin in Lead V_1, both as to duration of the Q wave and time of onset of the intrinsicoid deflection. Signs of the posterior extension were detectable in Case 69, because of an intermediate cardiac position favorable to the transmission of the potential variations of the posterior wall of the left ventricle to the left leg.

The standard leads showed classical signs of right bundle branch block in ten cases, atypical signs in keeping with this diagnosis in two cases, and evidence pointing toward left bundle branch block in two cases. It is noteworthy that the findings in the standard leads were not sufficiently distinctive in any case to permit a definite diagnosis of septal infarction as the cause of the conduction defect.

3. *Left Ventricular Conduction Defects*: These defects were established from the following findings: QRS interval of 0.12 second or longer in complexes derived from impulses of supraventricular origin; prominent late R wave and abnormally delayed intrinsicoid deflection in leads from the left axilla, which reflected the potential variations of the epicardial surface of the left ventricle. The sixteen patients whose electrocardiograms conformed with the foregoing criteria were classifiable into two groups, in accordance with the direction of the first phase of the QRS complex in precordial leads over the left ventricle: (a) those in whom an initial R wave was present in all precordial leads over the left ventricle, six patients (Cases 77, 82, 99, 114, 125, and 136); (b) those in whom a Q wave was present in one or more precoridal leads over the left ventricle, ten patients (Cases 43, 46, 50, 57, 59, 78, 79, 80, 95, and 96).

(a) *Pattern characterized by a QRS interval of 0.12 second or longer, and an initial R wave and a late intrinsicoid deflection in precordial leads over the left ventricle* are usually due to activation of the septum and left ventricle by impulses starting from the Purkinje network beneath the endocardium of the right side of the septum and progressing from right to left. This mode of activation causes (1) early positivity of the left ventricular cavity and thus an initial upstroke in precordial leads over the left ventricle; (2) late arrival of the impulse at the epicardial surface of the entire left ventricle, especially in its lateral and posterior aspects, with consequent prolongation of the ascending limb of the R wave and delay in the onset of the intrinsicoid deflection in left axillary leads.

From a study of the electrocardiographic and pathologic findings in Cases 77 and 125, it was concluded that the prolongation of the QRS complex in these cases was probably not due to the foregoing mechanism. The tracings were obtained four and twenty-three hours, respectively, after the onset of the pain and were followed shortly by death, with demonstration of an infarct of less than twenty-four hours' duration in the septum and lateral wall of the left ventricle. Although an initial upstroke was found in Leads V_4 through V_6, a distinct Q wave was recorded in left ventricular Lead aV_L of both patients, indicating that the left ventricular cavity was initially negative and that the vector associated with septal activation pointed toward the right rather than than the left. Furthermore, the prolongation of the monophasic upright QRS complex recorded in Leads V_4 through V_6 of both patients appeared to be due more to spreading of the descending limb than to delay in the attainment of the peak of the R wave. These findings indicated that the lengthened QRS interval was due to the lateral, rather than the septal, portion of the lesion and were in keeping with an early infarct which had retarded, but not obliterated, the response to the activating impulse.

In the other four cases, the initial phase of the QRS complex was upright, not only in precordial leads over the left ventricle, but also in Lead aV_L, and the pattern conformed with that customarily attributed to left bundle branch block. Since the septal portion of the infarct was limited to the apical one-third in Cases 99 and 114 and to the apical one-half in Case 82, the conduction defect was probably due to a separate lesion in the left branch of the bundle of

His. An alternative explanation for the electrocardiographic findings in Case 81 was suggested by the pathologic demonstration of an acute infarct limited to the left side of the apical two-thirds of the septum. An infarct in this position may have interfered with spread of the impulse through the left Purkinje plexus into the septum and thus indirectly favored activation of the septum by impulses distributed through the right Purkinje plexus. This would have reversed the vector associated with septal activation, causing early positivity of the left ventricular cavity and thus an initial upstroke in leads over the left ventricle. A comparable reversal in direction of activation of septal remnants seemed the best explanation for the initial R wave recorded in all leads over an extensive transmural anterolateral infarction in Case 34, despite a QRS interval of only 0.10 second.

(b) *Patterns characterized by a QRS interval of 0.12 second or longer and an initial Q wave and late intrinsicoid deflection in precordial leads over the left ventricle* may be produced by (1) a conduction defect in the free wall of the left ventricle, resulting from dense infarction of the subendocardial portion and patchy infarction of the mid-zone and subepicardial layer; (2) left bundle branch block associated with a large septal infarct and accompanied by infarction of at least the deeper portion of the free wall of the left ventricle. Consideration will be given to the probable mechanism of production of the electrocardiographic findings in both types of conduction defect, prior to an analysis of the findings in the ten patients exhibiting these patterns, along with pathologic evidence of infarction of the septum and free wall of the left ventricle.

Abnormal QR complexes, delayed onset of the intrinsicoid deflection, and prolongation of the QRS interval were found in Cases 21, 45, 141, 154, and 155 as a manifestation of infarction involving the free wall of the left ventricle, but not the septum, and could be correlated with a lesion that was dense in the subendocardial layer and patchy in the more superficial portion of the myocardium. The downward component of the abnormal QR complex characteristic of infarction, distributed in the foregoing manner, represents negative cavity potentials transmitted to the overlying precordium while the impulse is making its way through the unresponsive subendocardial layer, whereas the succeeding upward component represents positive potentials referred to the surface after the impulse reaches and begins to activate living muscle in the mid-zone or subepicardial layer. Slurring or notching of the ascending limb of the R wave and prolongation of time interval from its onset to peak are prone to occur when the living muscle in the mid-zone or subepicardial layer is split up into islands by patches of dead muscle or fibrous tissue. The registration of a Q wave while the impulse is held up in the densely infarcted subendocardial muscle and a prolonged R wave during its retarded passage through patches of living muscle in the more superficial layers accounts for the lengthening in the interval preceding the intrinsicoid deflection and is an important factor in the prolongation of the QRS complex.

When left bundle branch block is accompanied by infarction of a portion of the septum, the left ventricular cavity receives positive potentials produced by activation of the intact remnants of septum and, at the same time, negative

potentials produced by activation of the right ventricle and transmitted to the right ventricular cavity and through the infarcted portion of the septum. The resultant initial potential of the left ventricular cavity depends first, upon the relative size of the infarcted and intact portions of the septum, and second, upon the magnitude of the negative potentials available for transmission through the septal infarct. Since the negative potentials referred to the right ventricular cavity during activation of its thin outer wall are much less than those referred to the left ventricular cavity during activation of its thick outer wall, one would surmise that a much greater septal destruction would be necessary for preponderant initial negativity of the left ventricular cavity in the presence of left bundle branch block than for preponderant initial negativity of the right ventricular cavity in the presence of right bundle branch block. Complicating right ventricular hypertrophy should accentuate the negative potentials transmitted through the infarcted septum in the presence of left bundle branch block and thus should favor the registration of Q waves in left ventricular leads. Furthermore, the recording of Q waves under these circumstances not only requires septal infarction of sufficient size to lead to initial negativity of the left ventricular cavity, but also infarction of at least the deeper portion of the myocardium beneath the exploring electrode.

In ten patients with a QRS interval of at least 0.12 second, an abnormal Q wave, and a late intrinsicoid deflection in left ventricular leads, infarction of both the septum and free wall of the left ventricle was demonstrated at autopsy and the question arose as to the site of the conduction defect.

Left bundle branch block was suggested by the findings in the standard limb leads in Case 78, but could be excluded indirectly by the demonstration of definite signs of right bundle branch block in the precordial leads, together with a normal P-R interval. If left bundle branch block also had been present, A-V block should have resulted. A small Q wave and a broad R wave were recorded in Lead aV_L, but only the upright phase carried over into Lead I, creating the false impression of left bundle branch block. The QR pattern in Leads V_5, V_6, and aV_L of this patient was not a manifestation of right bundle branch block, because of differences in contour and time of onset of intrinsicoid deflection from that in right ventricular Leads V_1 and V_2, and thus, by exclusion, was ascribed to a conduction defect in the free wall of the left ventricle. The distribution of the lesion in the anterolateral aspect of the left ventricle confirmed these conclusions.

Left bundle branch block was considered very unlikely in Cases 43, 57, 59, 79, 95, and 96 because of the registration of distinct Q waves in left ventricular leads (indicating early negativity of the left ventricular cavity), together with a small initial R wave and a prominent S wave in Lead aV_R (pointing to early positivity of the right ventricular cavity). However, left bundle branch block could not be excluded positively by these findings, since the initial R wave in Lead aV_R might have been transmitted from the epicardial surface of the right ventricle, rather than from the cavity. The potential variations of the posterobasal portion of the left ventricle were referred to the right arm in Cases 46, 50, and 80, but the registration of normal initial R waves in leads from the

right precordium in the two former cases was somewhat against initial negativity of the right ventricular cavity secondary to left bundle branch block.

The septal infarct was excluded as a cause of the electrocardiographic findings in Cases 43 and 96, by reason of its limitation to the left side of the apical one-third of the septum. Localization of the conduction defect in the free wall of the left ventricle of these cases was supported by the close correspondence between the abnormal QR patterns and the distribution of the lesion in the underlying myocardium. It is noteworthy that a QRS interval of 0.16 second in Case 96 was apparently referable to a conduction defect in the free wall of the left ventricle.

The infarcts in Cases 46, 57, 79, and 95 involved approximately one-half of the septum and were thus comparable to the smallest infarcts in this series that had produced right bundle branch block. For reasons already given a larger septal infarct would probably be needed for initial negativity of the left ventricular cavity in the presence of left bundle branch block than for initial negativity of the right ventricular cavity in the presence of right bundle branch block. Since half of the septum was spared in each of these four cases, initial R, instead of Q, waves would have been expected in left ventricular leads if left bundle branch block had been present. Because of the aforementioned evidence against left bundle branch block together with the close correspondence between the QR patterns and the distribution of the lesion in the free wall of the left ventricle, it was concluded that the conduction defect in these cases was in the free wall. However, it must be admitted that a conduction defect in the septum could not be excluded positively.

The lesion in Cases 50, 59, and 80 involved two-thirds or more of the septum and thus was considered large enough to have accounted for initial negativity of the left ventricular cavity, if left bundle branch block had been present. The apparent initial positivity of the right ventricular cavity in the two latter cases was against the presence of left bundle branch block, but the initial negativity in Case 50 was compatible. However, if the extensive septal destruction in these patients had been complicated by left bundle branch block, a longer QRS interval would have been anticipated than the measurement of 0.12 second in Cases 50 and 80 and 0.13 second in Case 59. Since the pattern in leads facing the epicardial surface of the left ventricle of all three patients corresponded satisfactorily with the distribution of the lesion in the underlying myocardium, a conduction defect in the free wall was favored.

4. *Q Waves and/or Displacement of the RS-T Segment in Leads From the Right Precordium, in the Absence of Bundle Branch Block*: Activation of the septum and activation of the anterior wall of the right ventricle are jointly responsible for the initial R wave normally found in leads taken with the exploring electrode applied to the precordium over the right ventricle or atrium and repolarization of these structures presumably has the predominant effect upon the RS-T segment and T waves in the same leads. When the heart is in horizontal position, Lead aV_F reflects chiefly the potential variations of the right side of the septum and posteroinferior wall of the right ventricle and is thus comparable to leads from the right precordium. Infarction of the septum,

in the absence of bundle branch block, may cause changes in the QRS and/or RS-T complex in right ventricular leads, which are classifiable into three main groups: (a) triphasic QRS complex, consisting of a small Q, small R, and deep S wave, with or without abnormal displacement of the RS-T segment; (b) monophasic QS deflection, with or without displacement of the RS-T segment; (c) normal RS complex with abnormal displacement of the RS-T segment.

(a) *Triphasic QRS complex in right ventricular Leads V_1 and/or V_2, characterized by a small Q, small R, and deep S wave in the absence of right bundle branch block** was encountered in one case of primary septal infarction (Case 83) and in three cases of septal extension of large anteroposterior infarction (Cases 50, 66, and 152). This pattern was well correlated with the pathologic demonstration of a healed infarct of the left side of the septum in Cases 66 and 152. The initial Q wave reflected early negativity of the right ventricular cavity, presumably due to activation of the preserved right half of the septum by impulses distributed through the right Purkinje system before impulses distributed through the corresponding network beneath the left ventricular endocardium could traverse the infarct and reach intact septal muscle. The succeeding R wave may have been due entirely to activation of the free wall of the right ventricle or partially to activation of septal remnants by impulses which finally arrived by way of the left-sided Purkinje system. The deep S wave represented negative potentials of the left ventricular cavity transmitted to the right precordium after depolarization of the septum and free wall of the right ventricle.

Right ventricular Lead V_1 in Case 50 displayed a 1.0 mm. Q wave, a 4.0 mm. R wave, and a slightly larger S wave. Autopsy disclosed a large, healed anterolateral infarct which involved the entire apical one-third of the septum, the left half of the middle third, and also crossed over to include a part of the anterior wall of the right ventricle. After the pathologic examination had been completed, the question arose as to whether the septal or right ventricular portion of the infarct was responsible for the Q wave in Lead V_1. Upon further reflection, it was evident that the Q wave could not have been due primarily to the right ventricular portion of the infarct, since activation of the septum in the usual fashion would have resulted in early positivity of the right ventricular cavity and thus an initial R wave in precordial leads over the right ventricle, irrespective of whether or not its free wall was infarcted. The pattern in Lead V_1 of this patient could be correlated with the distribution of the lesion in the middle third of the septum.

A small Q, small R, and deep S wave, with a normal QRS interval, were found in Leads V_1 and V_2 in Case 83, as a manifestation of an old healed infarct, practically confined to the apical half of the septum and distributed in patchy fashion between the two endocardial surfaces. This finding, together with a normal RS pattern in left ventricular Leads V_3 through V_6, led to an ante-mortem diagnosis of infarction localized to the interventricular septum.

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*A triphasic QRS complex, consisting of a Q, a late R, and a terminal S wave, may be observed in leads near the transitional zone in right bundle branch block due to septal infarction, as exemplified by Lead V_2 in Case 75. This and other comparable cases have been classified separately and discussed previously and therefore will receive no further consideration.

Before a triphasic QRS complex with an initial Q wave in Lead V_1 and/or V_2 is attributed to septal infarction, other possible causes must be considered and excluded in the differential diagnosis. A pattern conforming to this general description may be found as a manifestation of uncomplicated left bundle branch block, right ventricular hypertrophy, and infarction of the free anterior wall of the left ventricle accompanied by displacement of the transitional zone to the right.

In left bundle branch block, irrespective of the presence or absence of septal infarction, right ventricular Leads V_1 and V_2 may display a Q wave, representing initial negativity of the right ventricular cavity due to reversal in the vector associated with septal activation; a minute R wave produced by passage of the impulse through the subjacent free wall of the right ventricle; and a final deep, broad S wave, reflecting negative potentials transmitted from the left ventricular cavity. Activation of the free wall of the right ventricle, in some cases of uncomplicated left bundle branch block, gives rise to a notch or mere slurring near the beginning of the downstroke of the fused Q and S deflections in these leads. Thus, in cases of left bundle branch block, the presence or absence of septal infarction cannot be determined from the contour of the QRS complex in right ventricular leads.

In uncomplicated right ventricular dilatation and hypertrophy, leads near the transitional zone may display a triphasic QRS complex, beginning with a small Q wave. The transitional zone is often broad in right ventricular dilatation and hypertrophy and may be displaced sufficiently to the right to include Positions V_1 and V_2, as exemplified by the triphasic QRS complex recorded in these leads as a manifestation of uncomplicated right ventricular dilatation and hypertrophy in Case 19 of a previous communication.[26] The differentiation of such patterns from those due to septal infarction is facilitated by additional leads below and to the right of the customary positions, namely, Leads V_E and V_{3R}. The diagnosis of right ventricular hypertrophy can usually be established by the demonstration of a relatively large R wave and a late intrinsicoid deflection in leads to the right of the transitional zone, with or without a minute Q wave and a relatively small terminal S wave.

Abnormal QRS complexes might be recorded in Lead V_2, or even in V_1, as a manifestation of infarction of the free anterior wall of the left ventricle, if the transitional zone is displaced far to the right. This possibility could be excluded in Cases 50, 66, 83, and 152 by the presence of diphasic P waves, or upright P waves with steep terminal phase in Leads V_1 and V_2, indicating that the electrode was in the vicinity of the right atrium and hence was well to the right of the transitional zone.

When the heart is in the horizontal position, the potential variations of the right side of the septum and posteroinferior wall of the right ventricle are transmitted to the left leg and abnormalities referable to septal infarction may be found in Lead aV_F. A triphasic QRS complex, consisting of a small Q wave, a small R wave, and a deep S wave, was recorded in Lead aV_F in Cases 60, 101, and 102 and could be correlated with infarction of the posterior part of the septum demonstrated at autopsy. The small Q wave probably represented initial

negativity of the right ventricular cavity, as a result of activation of the preserved right side of the posterior portion of the septum by impulses distributed through the right Purkinje system, whereas the small R wave was probably due largely to activation of the remainder of the septum by impulses distributed through the left Purkinje system. Activation of the posterior wall of the right ventricle probably contributed little toward the R wave in these cases, since the infarct continued into this portion of the heart. On the other hand, the infarct of the posterior wall of the right ventricle could not have been primarily responsible for the Q wave in Lead aV_F, since activation of the septum in the normal fashion should have produced initial positivity of the right ventricular cavity and thus an R wave in Lead aV_F, irrespective of the presence or absence of infarction of the free wall of the right ventricle.

(b) *Monophasic QS complex in both Leads V_1 and V_2* was found in one patient with primary septal infarction (Case 84), in fifteen patients with septal continuation of a large anterolateral or anteroposterior infarction (Cases 24, 25, 26, 29, 30, 37, 39, 40, 41, 49, 51, 53, 59, 65, and 91), and in one patient with extension from posterior infarction (Case 89). The lesion involved the apical two-thirds or more of the septum in thirteen cases, the apical one-half in three, and was limited to the left side of the posterior part of the septum in Case 89. Enough of the septum had been destroyed in all patients except Case 89 to account for the QS complexes in Leads V_1 and V_2 by the assumption that negative left ventricular cavity potentials transmitted through the septal infarct to the right precordium exceeded positive potentials coming from activation of septal remnants together with the free wall of the right ventricle. Before such an explanation could be accepted, it was necessary to consider other possible causes for the registration of QS patterns in leads from the right side of the heart.

A QS complex in both Leads V_1 and V_2 is not, in itself, diagnostic of septal infarction, since it is found in uncomplicated left bundle branch block, in left ventricular hypertrophy, and even in occasional normal hearts.[27] Left bundle branch block is often manifested by a QS complex in right ventricular leads, for reasons already discussed, but was not responsible for that found in any of the foregoing seventeen cases. The registration of a QS complex in Leads V_1 and V_2 in normal subjects and in patients with left ventricular hypertrophy is favored by a cardiac rotation which brings the right atrium beneath the sternum, carries the left apex backward, and tilts the mitral orifice to the right and forward. Such a position facilitates transmission of left ventricular cavity potentials toward the right atrium and may lead to a QS complex in Leads V_1 and V_2 when the negative potentials reaching the precordium through the above route exceed the positive potentials coming from activation of the septum and free wall of the right ventricle.

The ante-mortem decision as to whether QS complexes in Leads V_1 and V_2 are the result of septal infarction or merely a normal variant depends upon (1) the level of the RS-T junction and the contour of the segment in Leads V_1 and V_2, and (2) the QRS pattern in leads to the right and left.

The former criterion may be useful during the acute stage of infarction, but is of little or no aid after healing. Upward displacement of the RS-T junc-

tion, together with upward concavity of the RS-T segment in Leads V_1 and V_2, is a common finding in left ventricular hypertrophy, but may also occur in association with infarction. The combination of abnormal elevation of the RS-T junction and upward convexity or straightening of the segment in Lead V_1 and/or V_2 in Cases 24, 25, 26, 30, and 53 pointed toward recent infarction and corresponded satisfactorily with the post-mortem findings. However, a comparable pattern in Cases 49 and 84 was traceable to digitalis action, rather than acute infarction. Thus, the evidence furnished by the RS-T pattern in Leads V_1 and V_2 is of limited value.

The presence of a normal initial R wave in Lead V_{3R} indicates that a QS pattern in Leads V_1 and V_2 is the result of infarction and not a normal variant.[18] The abnormal Q waves demonstrated in leads farther to the left in sixteen cases (all except Case 89) constituted indirect evidence that the QS complexes in Leads V_1 and V_2 were also the result of infarction. The QS pattern in Leads V_1 through V_3 in Case 84 could be correlated with the pathologic demonstration of a large infarct practically limited to the septum. However, in the other fifteen cases, the question remained as to whether the QS pattern in Leads V_1 and V_2 was a manifestation of the septal or the anterior portion of the infarct.

The contour of the P wave in Leads V_1 and V_2 was utilized as an index of the position of the electrode in reference to the cardiac surface. The registration of a steep intrinsicoid downstroke in the P waves in Cases 26, 29, 30, 37, 39, 40, 41, 51, 53, 59, and 65 indicated that the electrode in precordial Positions 1 and 2 was in the vicinity of the right atrium and that the QS patterns were referable to infarction of the septum, rather than to that of the free anterior wall of the left ventricle. The presence of auricular circus movement in Cases 25 and 49 and of low voltage P waves in Cases 24 and 59 left the position of the electrode in reference to the cardiac surface in doubt and hence left the question open as to whether the QS complexes in Leads V_1 and V_2 were a manifestation of the septal or the anterior portion of the infarct. Because of the extreme rarity of the preponderant registration of the potential variations of the anterior wall of the left ventricle in Lead V_1, it is probable that the QS patterns in this lead in Cases 24, 25, 49, and 59 were likewise due to the septal portion of the infarct.

A monophasic QS complex in Lead V_2 in association with an RS complex in Lead V_1 was found in eight cases of anterolateral infarction, which continued into the septum. An unequivocal diagnosis of infarction could be made from the findings in Lead V_2, together with the initial R wave in Lead V_1 and the abnormal Q waves in leads farther to the left. The diphasic P waves in Lead V_2 in Cases 33 and 57 and the upright P waves with steep terminal limb in Cases 27, 62, and 79 indicated that the electrode was in the vicinity of the right atrium and thus reflected the potential variations of the right side of the septum and right ventricle, rather than those of the anterior wall of the left ventricle. The QS complex in Lead V_2 in these five cases was therefore attributed to the septal, rather than the anterior, portion of the infarct. The contour of the P wave in Lead V_2 in Cases 32 and 52 indicated that the electrode lay beyond the right atrium, but gave no information as to whether it was over the right or left ventricle. The

major source of the ventricular complex in Lead V_2 was also indeterminate in Case 48 because of the presence of fine auricular fibrillation.

Monophasic QS complex in right ventricular Lead aV_F of a horizontally placed heart may occur as a manifestation of septal infarction, of left bundle branch block, or as a normal variant. The QS complex in Lead aV_F in Cases 85, 100, and 111 was believed referable to the septal infarct because of the abnormal slurring or notching and prolongation of the descending limb, and that in Case 53 was attributed to the acute septal infarct because of the accompanying RS-T pattern. More detailed discussion of the findings in Lead aV_F will be reserved for a subsequent manuscript.

(c) *Abnormal displacement of the RS-T segment in Lead V_1 and/or. V_2, suggesting recent infarction*, was found in association with a normal initial R wave in five cases of acute infarction of the septum and anterior wall of the left ventricle (Cases 23, 34, 61, 77, and 80) and in two cases of acute posteroseptal infarction (Cases 87 and 88). Although an epicarditis of the anterior wall of the right ventricle, secondary to extension of the pericarditis accompanying acute left ventricular infarction, is a possible cause for displacement of the RS-T segment in right ventricular leads, it was not responsible for the pattern in Leads V_1 and V_2 of any of these seven cases. The changes of the RS-T segment in Cases 87 and 88 were believed referable to the acute infarct of the posterior half of the septum and the initial R wave in Leads V_1 and V_2 was probably derived from the intact anterior half of the septum and free wall of the right ventricle. The RS-T changes in the other five cases could be correlated with the extensive acute infarct of the septum. The preservation of the R wave in Cases 77 and 23 could be explained by the fact that the tracings were obtained only four and twelve hours, respectively, after the onset of symptoms. The large septal lesion in the other three cases should have permitted transmission of negative left ventricular cavity potentials to the right precordium sufficient to counterbalance the positive potentials coming from activation of septal remnants and the free wall of the right ventricle and thus should have led to an initial Q wave in Leads V_1 and V_2. The registration of an initial R wave in these leads was probably due to a marked reduction in opposing left ventricular cavity potentials secondary to extensive infarction of the free wall of the left ventricle.

5. *Absence of Direct Evidence of Septal Infarction.*—The findings in leads facing the right side of the septum and epicardial surface of the right ventricle (precordial leads to the right of the transitional zone and, in addition, Lead aV_F in horizontally placed hearts) that constitute direct evidence of septal infarction have been discussed at length. In brief summary, these findings are: (1) right bundle branch block, characterized by an abnormal Q wave and/or a classical RS-T pattern; (2) a triphasic QRS, consisting of a small Q wave, a small R wave, and a deep S wave and occurring in the absence of right ventricular hypertrophy; (3) abnormal QS pattern accompanied either by a normal R wave in leads farther to the right or by abnormal Q waves in leads farther to the left. The findings in the same leads which may be regarded as suggestive of septal infarction are: (1) incomplete patterns fulfilling part, but not all, of the criteria in one of the three

foregoing categories; (2) classical displacement of the RS-T segment in Leads V_1 and V_2 without QRS abnormalities in these leads, but accompanied by abnormal Q waves in leads farther to the left. The combination of left bundle branch block and abnormal Q waves in left ventricular leads is also diagnostic of septal infarction, but could not be established definitely in any case in this series.

An analysis of the electrocardiograms of the six patients with pathologically demonstrated primary septal infarction revealed diagnostic evidence in four, consisting of classical right bundle branch block patterns in three and triphasic QRS in one; a strongly suggestive QS pattern in right precordial leads of one patient; and a QS pattern in right ventricular Lead aV_F compatible with septal infarction in one patient.

The septal extension of a large anterior or anteroposterior infarction was manifested by diagnostic electrocardiographic signs in twenty-nine cases, by suggestive signs in eleven, and by no direct evidence in the other nineteen cases. In nine of the latter group, leads from the precordium and left leg revealed signs of anteroposterior infarction. Since large anterior infarcts that continue into the posterior wall of the left ventricle almost invariably extend through the septum, electrocardiographic signs of an anteroposterior lesion constitute indirect evidence, presumptive of infarction of the intervening septum.[17] However, indirect evidence of this type cannot be regarded as diagnostic of septal infarction, since signs of involvement of the anterior and posterior walls may result from two separate lesions, neither of which extends into the septum, as in Case 68.

In analyzing the causes of diagnostic failure in the foregoing nineteen cases, it is noteworthy that no direct electrocardiographic evidence of septal infarction was found in any of the six patients in whom the septal extension was confined to the apical one-third (Cases 22, 42, 43, 64, 67, and 96). Since infarction of the apical one-half of the septum was detected electrocardiographically in eight of thirteen patients, it would appear that a lesion approaching this size represents the minimum necessary for diagnostic signs. However, direct electrocardiographic evidence of septal infarction was absent, not only in five patients with involvement of the apical half (Cases 46, 56, 58, 63, and 81), but also in eight patients with involvement of the apical two-thirds or more (Cases 31, 35, 36, 38, 47, 55, 82, and 151), including one patient with a large perforation (Case 55). Left bundle branch block was present in Cases 81 and 82, but the patterns were not diagnostic of septal infarction in either instance, even though the conduction defect was probably secondary to the septal lesion in the former. The absence of direct electrocardiographic evidence in Cases 36 and 38 was attributable to a very recent septal lesion of insufficient duration to obliterate the response to the activating impulse. The registration of initial R instead of Q waves in right ventricular leads of the remaining nine patients was considered an indirect effect of the extensive infarct of the free wall of the left ventricle. As a result of the latter, the negative potentials referred to the left ventricular cavity and thence through the septal infarct toward the right precordium were probably so reduced that they failed to counterbalance positive potentials coming from activation of the free wall of the right ventricle and from intact remnants of septum. Right

ventricular hypertrophy in Case 47 was an additional factor that contributed directly toward the initial upstroke recorded in Leads V_1 and V_2.

Septal extension of posterior infarction was indicated by the association of complete A-V block with signs of recent posterior infarction in Cases 88 and 104, but was manifested by abnormalities in the ventricular complex of Lead V_1 in only two of the twenty-four patients (Cases 87 and 88). These consisted of dome-like elevation of the RS-T segment in both cases and terminal right bundle-branch block in the former. The rarity of QRS abnormalities in right precordial leads was attributable to the fact that septal extensions from posterior infarction were almost invariably confined to the posterior one-third to one-half of the septum. On the other hand, QRS abnormalities referable to infarction of this portion of the septum were recorded in Lead aV_F in Cases 60, 100, 101, 102, and 111 as a result of horizontal position of the heart. Thus, electrocardiographic signs indicative of extension of a posterior infarct into the septum were found in only eight of the twenty-four patients. Bundle branch block was found in four additional patients, but was considered independent of the septal infarct. The remaining twelve patients displayed no evidence suspicious of the septal lesion.

Infarction of the right ventricle was not encountered as an isolated finding in any of the 161 cases. The closest approach was in a patient (Case 124) who was admitted with an acute infarct of the posterolateral wall of the left ventricle and five weeks later had a second attack, characterized by infarction of the entire apex of the right ventricle, the adjoining septum, and a small segment of the posteroseptal wall of the left ventricle. An electrocardiogram made two hours after the second attack showed no change in the QRS pattern, but displayed increased upward bowing of the RS-T segment in Lead aV_F and reciprocal RS-T depression in Leads V_3 through V_6 and in Lead aV_L. These changes were indistinguishable from those produced by acute infarction limited to the posteroseptal wall of the left ventricle. Continuation of an infarct of the posterior wall of the left ventricle across the septum into the posterior wall of the right ventricle was demonstrated pathologically in twelve other patients (Cases 35, 38, 52, 60, 87, 88, 90, 100, 101, 102, 104, and 114), but was not manifested by electrocardiographic signs distinctive of the right ventricular lesion in any case. Extension of an infarct of the anterior wall of the left ventricle across the septum into the anterior wall of the right ventricle was demonstrated pathologically in six patients (Cases 11, 50, 54, 71, 72, and 79), but was not manifested by distinctive electrocardiographic signs, except, perhaps, in Case 71. The marked elevation of the RS-T junction in right ventricular leads in this case may have been due, in part, to acute injury to the anterior wall of the right ventricle.

SUMMARY

Infarction of the interventricular septum was demonstrated pathologically in 102 cases, which represents an incidence of 63 per cent in a series of 161 cases. The findings in thirteen cases of localized anteroseptal infarction were analyzed in a previous report. The present study is concerned with a correlation of electrocardiographic and pathologic findings referable to the septal lesion in the remain-

ing eighty-nine cases. These cases were classified into three groups, according to the distribution of the lesion at autopsy: Group A, infarction primarily in and largely confined to the septum in six cases; Group B, septal extension of large anterior or anteroposterior infarction in fifty-nine cases; Group C, septal extension of posterior infarction in twenty-four cases.

The following electrocardiographic patterns could be correlated directly with the septal infarct found at autopsy:

1. Complete A-V block was observed as a manifestation of extension of an acute posterior infarct into the base of the septum in two cases.

2. A QRS interval of 0.12 second or more, a prominent late R wave, and a delayed intrinsicoid deflection in leads from the right precordium were found in fourteen cases and were attributable to septal infarction in thirteen of the group because of the presence of a distinct Q wave and/or abnormally elevated RS-T junction in these leads. The infarct was confined to the apical one-half to two-thirds of the septum in five of the cases and probably caused delay in right ventricular activation by interruption of conduction through the right Purkinje system, rather than the right bundle branch. Since the electrocardiographic findings in these cases were similar to those in other cases with infarction reaching the anatomic site of the bundle of His, the customary term, "right bundle branch block," was retained to designate the conduction defect. The abnormal Q wave in right ventricular leads constituted the chief distinguishing feature from uncomplicated right bundle branch block and was recorded because of the preponderance of negative potentials transmitted from the left ventricular cavity through the infarcted septum to the right precordium over reduced positive potentials coming from activation of intact remnants of septum. The differentiation of infarcts limited to the septum from those continuing into the anterior wall of the left ventricle depended upon the QRS pattern in leads to the left of the transitional zone and was rendered difficult in three of the cases of right bundle branch block by displacement of the transitional zone into the left axilla. The recognition of extension of a septal infarct into the posterior wall of the left ventricle was possible from Lead aV_F in intermediate to vertical cardiac position, but not in transversely placed hearts, since reference of the potential variations of the right side of the septum to the left leg, as a result of horizontal position, produced patterns in Leads aV_F, II, and III which simulated those caused by posterior infarction. The standard limb leads did not reveal diagnostic evidence of septal infarction in any of the thirteen cases.

3. A QRS interval of 0.12 second or more, an initial upstroke in all leads facing the left ventricle, and an abnormally delayed intrinsicoid deflection in left axillary leads were found in four cases and were attributed to left bundle branch block independent of the septal infarct in three of these. In the remaining case, autopsy revealed an acute infarct limited to the left side of the apical two-thirds of the septum and the subendocardial layer of the anterior and posterior walls of the left ventricle, and the pattern was attributed to septal activation by impulses distributed through the right Purkinje plexus.

4. Patterns characterized by a QRS interval of 0.12 second or more, an initial Q wave, and a late intrinsicoid deflection in precordial leads over the left

ventricle were found in ten cases and were definitely attributable in three of these to an infarct of the free wall that was dense in the subendocardial layer and patchy in the more superficial portion of the myocardium. This explanation was favored in the other seven cases, but the alternative possibility of left bundle branch block due to extensive septal infarction could not be positively excluded.

5. A triphasic QRS complex of normal duration, characterized by a small Q wave, a small R wave, and a deep S wave, was found in right ventricular Leads V_1 and/or V_2 in four cases and was well correlated with the distribution of the septal infarct at autopsy. These findings may be considered diagnostic of septal infarction, provided right ventricular hypertrophy can be excluded. A similar pattern was found in Lead aV_F in three other cases and could be correlated with infarction of the posterior part of the septum. The potential variations of the right side of the septum were transmitted to the left leg in these cases because of horizontal position of the heart.

6. A monophasic QS complex of normal duration, found in Leads V_1 and V_2 or in V_2 in twenty-four cases, was regarded as a manifestation of infarction, rather than as a normal variant, because of the presence of one or more of the following findings: an abnormal upward displacement of the associated RS-T segment, a normal initial R wave in leads farther to the right, or abnormal Q waves in leads farther to the left. The abnormal QS complexes in Leads V_1 and V_2 in most of the cases were attributable to infarction of the septum, rather than infarction of the free anterior wall of the left ventricle, because of the presence of an intrinsicoid deflection in the accompanying P wave, indicating that the electrode was in the vicinity of the right atrium and thus faced the right side of the septum and right ventricle. The replacement of the initial R wave by a QS complex could be correlated with septal infarction that permitted transmission of left ventricular cavity potentials to the right precordium. An abnormal QS deflection in Lead aV_F, found in four patients with horizontally placed hearts, was believed referable to septal infarction.

7. Abnormal RS-T displacement, consistent with recent infarction, was found in right ventricular Leads V_1 and/or V_2 in association with normal initial R waves in seven cases. This finding could only be regarded as suggestive of septal infarction during life, but was believed referable to the recent septal infarct found at autopsy in each case.

Diagnostic or suggestive evidence of septal infarction was found in all six cases of primary septal infarction. Direct electrocardiographic evidence of the septal lesion was absent in sixteen of the twenty-four cases of septal extensions from posterior infarction, principally because of limitation of the lesion to the posterior one-third to one-half of the septum; and absent in nineteen of the fifty-nine cases of septal extension from anterior or anteroposterior infarction. The diagnostic failures were attributable to limitation of the infarct to the apical one-third of the septum in six of the latter group, to left bundle branch block in two, to a very recent septal lesion in two, and, in the remainder, to marked reduction in opposing negative potentials transmitted to the right precordium as a result of extensive infarction of the free wall of the left ventricle. In nine of the nineteen cases without direct electrocardiographic evidence of septal infarc-

tion, leads from the precordium and left leg revealed signs of anteroposterior infarction, which could be regarded as indirect evidence, presumptive of the presence of infarction in the intervening septum.

Isolated right ventricular infarction was not found in any case. Left ventricular infarcts continued across the septum into the posterior wall of the right ventricle in thirteen cases and into the anterior wall of the right ventricle in six others, but were not manifested by electrocardiographic signs distinctive of the right ventricular involvement in any case.

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A METHOD FOR RECORDING THE ARTERIAL PRESSURE PULSE AND BLOOD PRESSURE IN MAN

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THE ability to record accurately and to have immediately available tracings of arterial pressure pulses should be of value to the investigator and the clinician. Methods in current use for recording arterial pulse waves involve maintenance of a rigid needle in an artery, a requisite which limits the conditions under which pulse contours can be obtained. They also require the development of photographic paper before a tracing can be analyzed.

We propose to present a method for the continuous recording of pulse waves and blood pressure in man which has certain practical advantages over the techniques previously described. A small plastic catheter, inserted into an artery through a needle, is left in the artery when the needle is withdrawn. Attached to a capacitance manometer, this technique permits recording for long periods of time without discomfort and allows relatively free mobility of the subject. The record, received by an ink-writing oscillograph, permits continuous knowledge of blood pressure and provides an opportunity for observation of any changes in the contour of the pulse wave which may develop. The apparatus is compact, mobile, and flexible.

By comparing the contour of the pulse waves in the same subject under different conditions, one can obtain information concerning changes in stroke volume, vasoconstriction, or distensibility of the arterial system. Interpretations of this type will be illustrated by tracings obtained from a series of 100 patients studied to date.

METHOD

Accurate recording of pressure changes depends among other things on the selection of tubing of proper length and cross-sectional area. A small catheter is desirable from the standpoint of comfort, end pressure, turbulence, and capacity. The last must be considered since the smaller the capacity for a given length, the smaller will be the volume pressure changes with bending. Also the effective mass of fluid is reduced. Lead tubing has been used by others to secure flexibility between the artery and manometer and by comparison the effective mass of the latter becomes much larger. With underdamped systems of low natural frequency this factor becomes important in the possible produc-

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tion of overshoot. We use the Lilly capacitance manometer[1] which has a volume displacement of 10^{-6} ml. per 100 mm. Hg, thus permitting the use of small catheters.[2] This manometer is critically damped to 100 cyles per second.

The plastic catheters used in our apparatus are made from a synthetic polyvinyl resin.* The tubing as received from the manufacturers is quite flexible and elastic since it is intended for such application as electrical insulation. The flexibility is the desirable feature. The elasticity must be reduced to such a degree that it does not introduce a damping factor in the cardiovascular pressure ranges. This is accomplished by heating the plastic in an oven for seventy-two hours at 110° centigrade. Since the plastic is thermosetting, the tubing can, at the same time, be drawn out and set to any desirable length and diameter. The lower right insert in Fig. 1 pictures the device for drawing out this tubing. The entire device and tubing is placed in the oven. The catheters are drawn out to an outside diameter of about 0.45 mm. and an inside diameter of about 0.21 millimeter. At the end of the heating period they are cut into 12.0 cm. lengths with a sharp, nonhollow ground razor blade and stored in 1:1000 Zephiran chloride solution.

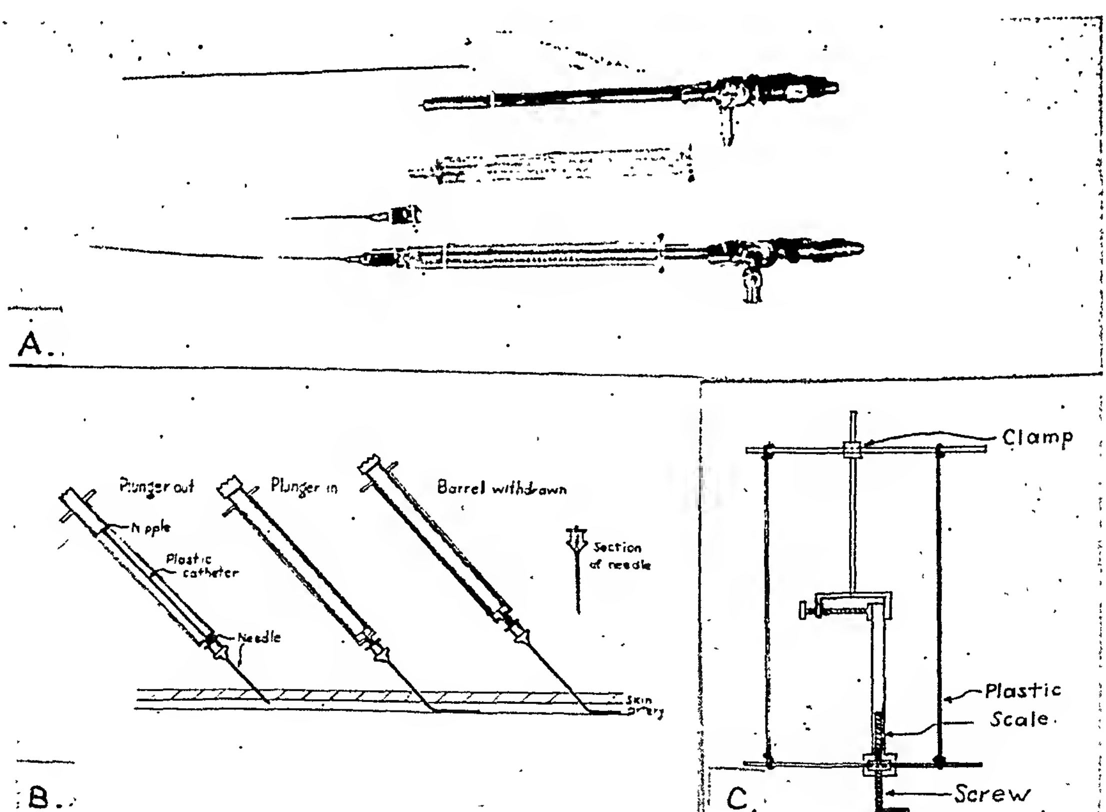

Fig. 1.—*A*, From above downward. Catheter, plunger, syringe, needle, and assembled device. *B*, Method of catheterizing. From left to right: arterial puncture made with plunger elevated, catheter injected into artery by pushing plunger down, entire device pulled back thus pulling needle out of tissue. Insert shows steel tubing projecting into hub of needle.

C, Adjustable rack for stretching plastic tubes a known distance and for maintaining this degree of stretch during baking.

*Manufactured by the Irvington Varnish and Insulator Company, Irvington, N. J.

Fig. 2.—A photograph to show the recording equipment, pick-up unit, and catheter. On the far right is seen the direct current amplifier and ink-writer. Not shown is the Lilly amplifier, calibration device, and fluid reservoir. The calibration tube is seen passing over the palm. Electrical lead and fluid tube can be seen entering the pick-up at right angles. Syringe barrel is seen attached to the pick-up through a three-way valve. The catheter is seen projecting from the needle and into the arm.

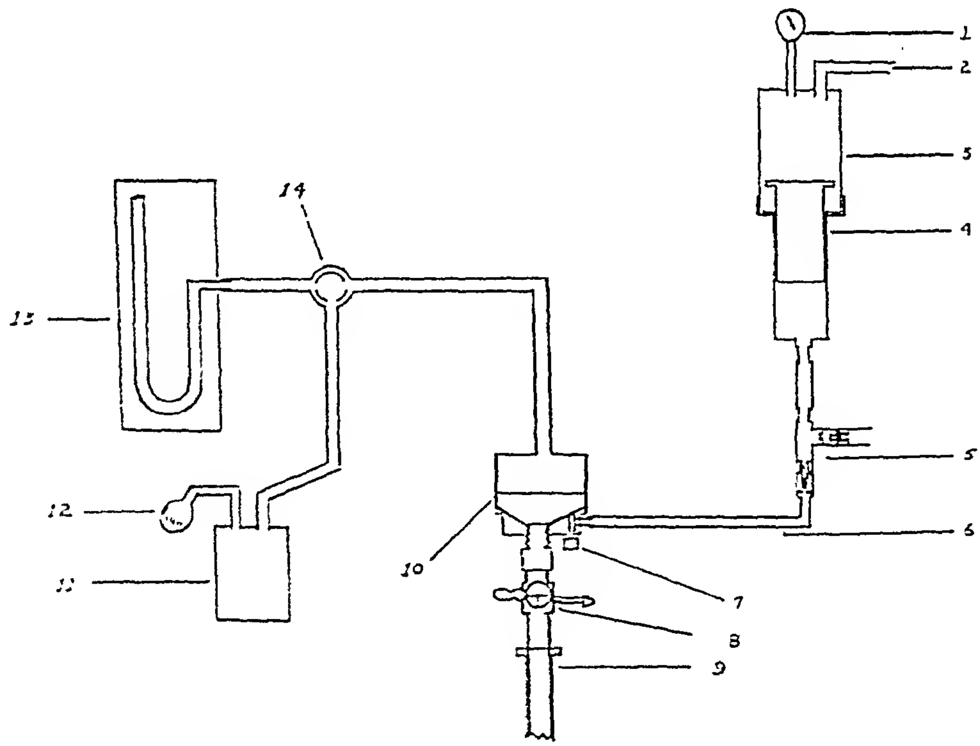

Fig. 3.—Schematic drawing of fluid and calibrating system. *1*, manometer; *2*, air pressure at about ten pounds per square inch; *3*, jacket around syringe; *4*, syringe and plunger; *5*, two-way B-D valve for filling; *6*, plastic tube to pick-up; *7*, needle valve for controlling flush; *8*, three-way B-D valve for recording base line; *9*, plunger for catheterization syringe; *10*, manometer diaphragm; *11*, calibration air pressure reservoir pumped up with *12*; *13*, mercury manometer for reading calibration pressure; *14*, three-way B-D valve for exposing the back of the membrane (*10*) to either atmospheric pressure or calibration pressure.

the end so that the pressure rises in the manometer. Sudden release of the occlusion reduces the pressure and gives an accurate enough recording of the relaxation time so that the presence of air is obvious. Fig. 4,*A* demonstrates such a test. The three curves on the left demonstrate the presence of air. During the recording time, the citrate reservoir under pressure remains attached to the manometer. Since most valves under pressure leak somewhat (1.0 ml. or less per hour) this insures that any leakage will be in the proper direction and that changes in blood pressure will not cause clotting. This does not affect significantly the pressure level or pulse curve. Sensitivity and base line calibrations are also made under the same circumstances.

The time relationships of the over-all response of the system are slightly longer than at critical damping. An interval of about 0.014 second is required

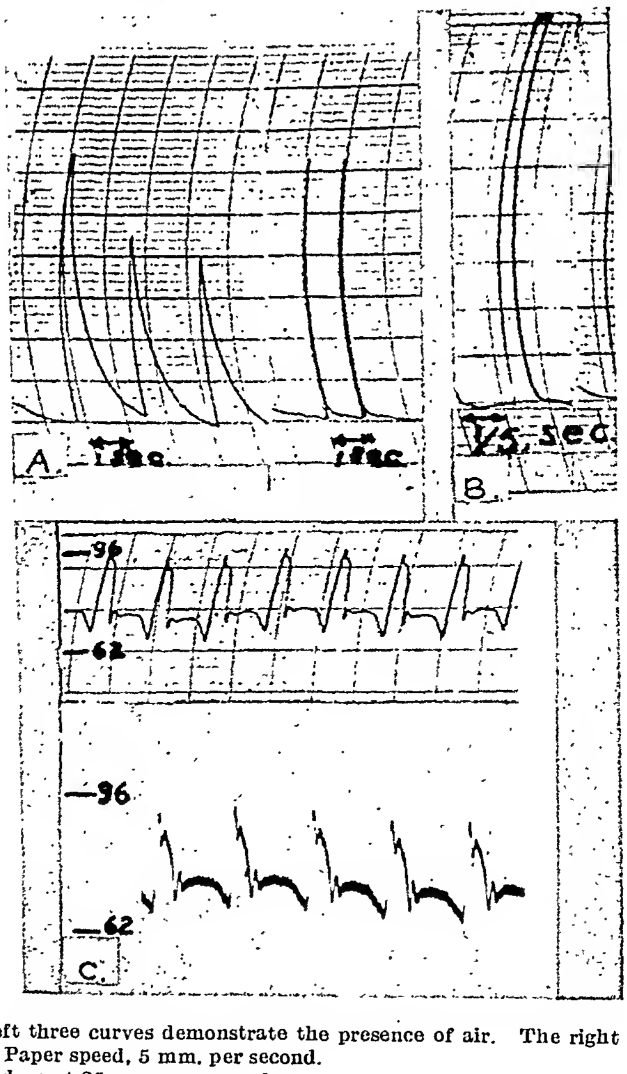

Fig. 4.—*A*, Left three curves demonstrate the presence of air. The right two, after the air has been flushed out. Paper speed, 5 mm. per second.

B, Same procedure at 25 mm. per second.

C, Comparison of ink-writer and camera records. The upper curve is recorded by the ink-writer. The lower is recorded photographically from a Kipp and Zonnen galvanometer, critically damped with a period of 0.01 second. These are simultaneous curves through the same catheter in the aorta of a dog 1.0 cm. from the aortic valves.

for 90 per cent relaxation by the method of Lilly.[3] It is felt that in the study of an unknown pressure pulse such an overdamped system eliminates the possibility of overshoot, provided the frequency response is the same as or faster than that of the unknown pressure pulse.

One hundred patients have been catheterized to date as described. The only discomfort is during the initial puncture. Visual recording provides immediate information that the artery has been entered; hence, arterial puncture is greatly facilitated. This fact and the practicability of a small bore needle reduces the initial discomfort to such a degree that no local anesthesia is necessary. The small size of the needle and catheter has sharply reduced the likelihood of hematoma formation. After withdrawal of the needle the presence of the catheter itself in the artery causes no sensation. Some of these patients have been followed continuously through the induction of anesthesia, during surgery, and in the postoperative period. Others have been studied under controlled physiological stresses. They ranged in age from 6 to 79 years and represented a wide variety of cardiorespiratory abnormalities. The environmental temperature during this study varied from 70 to 96° Fahrenheit.

It should be stressed that care must be exercised in avoiding occlusion of the artery from which the tracings are made. Errors in interpretation of records from the brachial artery, for example, might be serious if one overlooked occlusion of this vessel as the result of arm movements or from lying on the arm.[12] In addition, local effects in the circulatory bed of the vessel could cause erroneous assumptions of changes in the general circulation.

RESULTS

No attempt has been made to study thoroughly one particular type of circulatory disease. Nor has the action of any single drug or procedure been specifically analyzed. Experiments along these lines are being carried on at present. This report is designed to describe the method and to illustrate the utility of the apparatus in the recognition of imbalance of the circulation produced by changes in peripheral resistance, stroke volume, or distension of the vascular system.

1. *Peripheral Resistance.*—Fig. 5 demonstrates one sequence of events noted after the administration of a spinal anesthetic. This record is from a man, 72 years of age, who was scheduled for a suprapubic prostatectomy. The first tracing (7:45) is the preanesthetic pulse wave as recorded from the brachial artery. The second tracing (8:06) shows that a decided change has occurred in the circulatory system, yet systolic and diastolic levels have not altered greatly. Palpation and sphygmomanometric pressure measurements did not indicate the character or magnitude of the shift. This change is interpreted to mean predominantly a reduction in peripheral resistance and is similar to that reported by Volpitto and associates.[4] There is a rapid fall in the predicrotic limb of the pulse and the pressure has approached or reached diastolic levels before the incisura has appeared. Our experience indicates that with this change the general pressure levels may be maintained, provided no additional stress is

placed on the individual. The avoidance of additional stress is accomplished usually by seeing that the patient lies quietly and is undisturbed. Sometimes surprisingly small stimuli will cause a distinct decrease in blood pressure. In this case the skin incision, of which the patient was unaware, was followed by a reduction of about 25 mm. Hg in the systolic pressure.

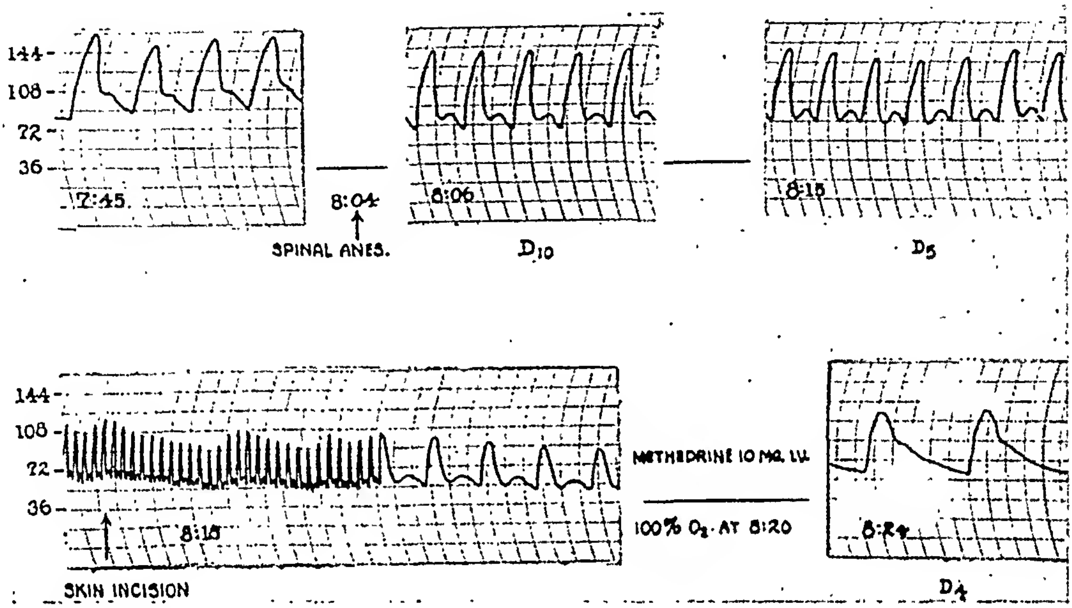

Fig. 5.—Pluse tracings from the brachial artery of a 72-year-old man.

7:45: Preanesthetic pulse wave. 8:04: Pontocaine Hydrochloride, 12.0 mg., given subdurally; no pressor drug given prior to induction. 8:06: Abolition of sensation to pin prick to the tenth dorsal dermatome (D-10). 8:14: Patient wheeled into operating room. 8:15: Abolition of sensation to D-5. Patient still lying quietly and undisturbed.

8:18: Methedrine, 10.0 mg., given intravenously; 100 per cent oxygen administered. 8:24: Abolition of sensation to D-4. Pressure pulse alteration due to administration of vasopressor drug and oxygen.

These records were traced with green ink on a red background; hence, they have been retraced for reproduction. Original line 0.1 mm. thick. Waviness of the lines are artifacts due to this retracing.

Horizontal lines equal 1.0 mm.; vertical lines equal 5.0 mm.; paper speed 25 mm. per second except first part of 8:18 tracing which is 5.0 mm. per second. Pressure scale on left margin in millimeters of mercury.

2. *Stroke Volume.*—Fig. 6 demonstrates a second cardiovascular change associated with spinal anesthesia. There is a hypodynamic rounded systole, in contrast to the sharp, unsustained pulse where the incisura approaches diastolic levels as seen in the previous figure. The postanesthetic pulse (9:20) is interpreted as representing a change primarily due to a reduced stroke volume and is similar to that reported by Wiggers.[5] The pulse is not collapsing and has no rapid fall of the predicrotic limb. With this alteration the pressure level cannot be maintained and will steadily fall despite the degree of quiescence of the patient.

Fig. 7 represents a case in which both of the changes previously mentioned occurred. This record was obtained from a woman undergoing a surgical procedure designed to remove a portion of the right lobe of the liver. The second tracing (8:01) demonstrates a change due to predominant reduction in peripheral resistance which followed the anesthetic. During the operation a tourniquet was

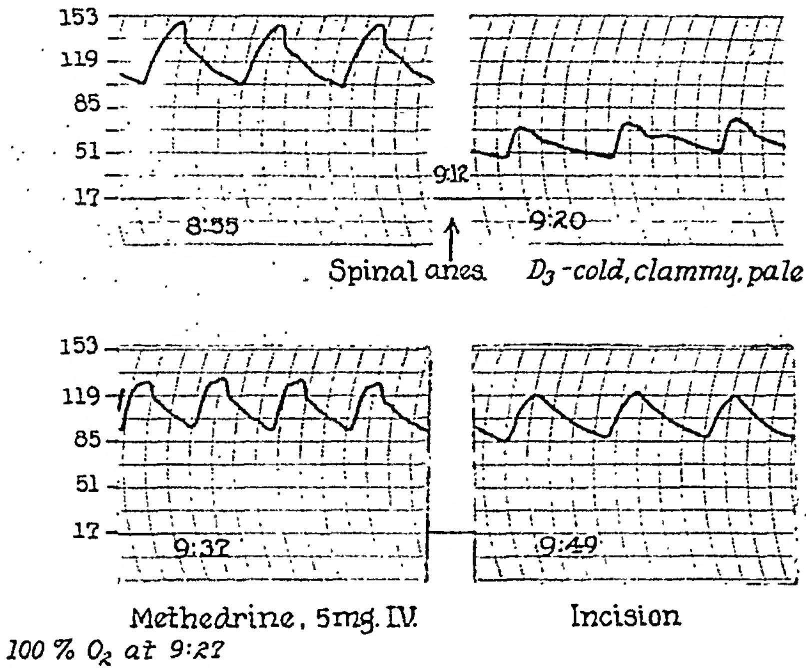

Fig. 6.—Brachial artery tracings from a 55-year-old man about to undergo an operation for bilateral inguinal herniorrhaphy. 8:55: Preanesthetic pulse tracing. 9:12: Pontocaine hydrochloride, 14 mg., given subdurally. No pressor drug given. 9:20: Postanesthetic tracing. The pressure levels fell concurrently with the formation of this type of pulse pattern. Abolition of pin prick sensation to D-4. Skin was pale, clammy, and cold.

9:27: Methedrine, 5.0 mg., administered intravenously. 9:36: Patient wheeled into operating room. 9:37: Pressure pulse ten minutes after administration of vasopressor drug. 9:49: Skin incision made. The pressure wave again assumed the character of the 9:20 figure and the pressure gradually fell as the vasopressor drug wore off.

Paper speed in all sections is 25 mm. per second. Pressure levels indicated at left margin.

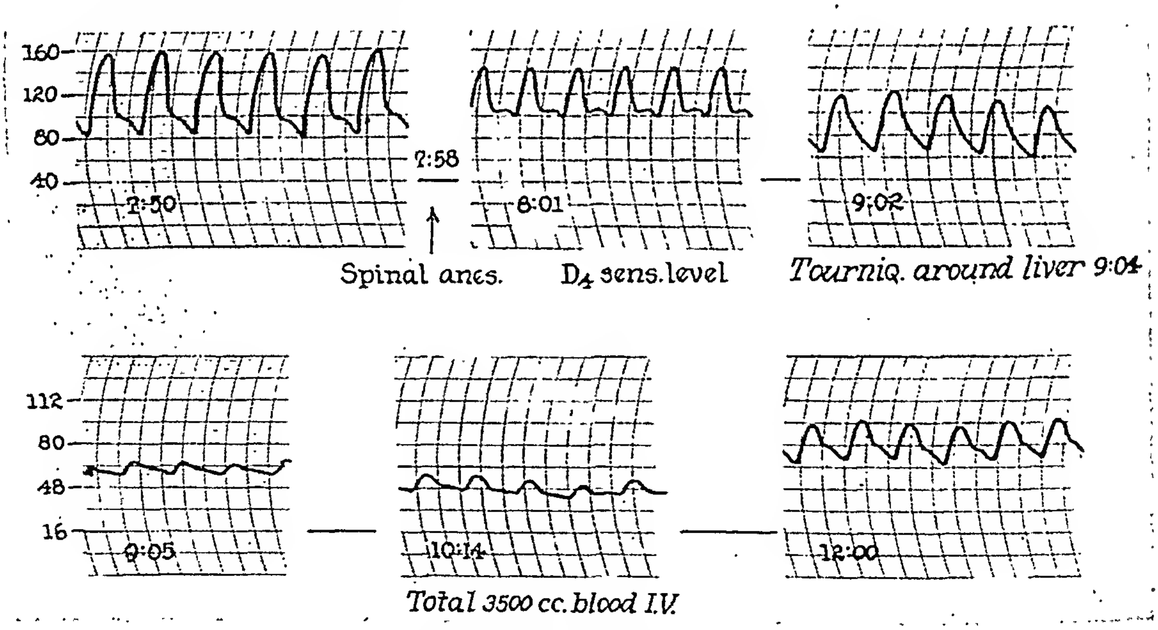

Fig. 7.—Brachial artery tracings from a 45-year-old woman about to undergo operation for partial removal of the liver. 7:50: Preanesthetic pulse. This patient had an oral temperature of 101.5° F. and was receiving chemotherapy and penicillin preoperatively. 7:58: Pontocaine hydrochloride, 12.0 mg., given subdurally. No pressor drug. 8:01: The base line in this section is at the bottom of the paper, whereas the base line of all other tracings is 5.0 mm. from the bottom. The same scale of pressure holds for the upper three tracings. Thus, the diastolic pressure is 80 mm. Hg and the systolic pressure is 124 mm. of mercury. Abolition of pin prick sensation at D-4.

8:05: Patient wheeled into operating room. 9:02: Prior to this tracing the pressure level had fallen and Methedrine had been given. 9:04: Tourniquet placed around liver and tightened thirty seconds later. The pressure fell from 130 systolic and 100 diastolic to that seen in the 9:05 tracings. 10:14: 3,500 c.c. blood had been given intravenously. 12:00: End of operation.

placed around the liver and tightened. In so doing, venous return was reduced as the result of occlusion of the inferior vena cava. There was a rapid fall in mean and pulse pressures, yet the pulse was full to the extent that the dicrotic limb did not drop rapidly. Removal of the tourniquet was followed by a rise in the blood pressure.

3. *Hemorrhagic Underdistention.*—Fig. 8 demonstrates a case in which the pulmonary vein was inadvertently cut with excessive hemorrhage. Here the mean and pulse pressures were low but with an unsustained type of pulse. There is a distinct difference in the character of this sort of underdistention and of that seen in Fig. 6, although both show approximately the same pulse rate and general pressure levels. Thus, underdistention due to hemorrhage could be distinguished from that of the previous example of reduced stroke volume under these conditions. Despite heroic transfusion therapy, this patient died on the operating table. There are other circulatory conditions which conceivably might produce similar curves. However, examination and previous control curves on the same patient will reduce this possibility to insignificance.

Fig. 9 is a series from the record obtained on a 42-year-old man with hypertension who had been subjected to a bilateral thoracolumbar sympathectomy and splanchnicectomy (approximately D-6 to L-3 inclusive) four months prior to this time. The patient was brought into the hospital for a study of the circulatory changes produced by such an operation. Included in this evaluation were simultaneous estimations of cerebral blood flow by the method of Kety and Schmidt[6] and of cardiac output by the ballistocardiogram.[7] Differential spinal anesthesia was produced as described by Sarnoff and Arrowwood.[8] This latter technique involves the subarachnoid injection of very dilute (0.2 per cent) concentrations of procaine in an attempt to block the small, relatively thinly myelinated vasomotor nerves and pain fibers, sparing conduction over somatic motor pathways entirely. In short, the method can rather closely approximate the end result expected from surgery as advocated by Smithwick, Grimson, and others for patients with hypertension.

This patient was tilted from the horizontal to a 70° head-up position on a tilting ballistocardiograph prior to receiving differential anesthesia. Some reduction in blood pressure occurred, but at the end of ten minutes of observation in the erect position, circulatory adequacy was still evident. A sensory level (to pin prick) of D-7 was then obtained with dilute procaine and the tilt repeated with the results noted in Fig. 9. The tilt caused lowered blood pressure, probably dependent on vasodilatation, and the absence of pulse acceleration noted in the previous tilt. As the erect position was maintained, the arterial pulse became less and less sustained and cerebral anemia with syncope and twitching occurred; three minutes after the tilt there was no visible heart beat on the tracing. Immediate return to the horizontal fortunately restored circulatory adequacy. The significance of this sequence of events will not be discussed in this paper, although some of its implications are of great interest. The value of continuous arterial pulse tracings under such circumstances is evident.

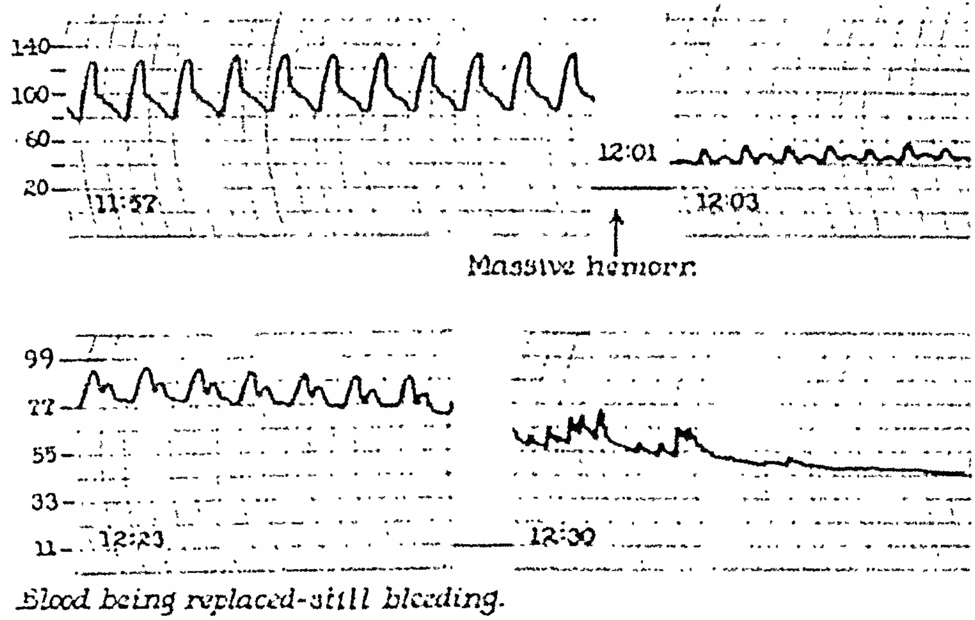

Fig. 8.—Brachial artery tracings from a 55-year-old man undergoing operation for bronchogenic carcinoma. Anesthesia induced at 9:55 with cyclopropane, ether, and oxygen. He was bronchoscoped at 10:05. Controlled respiration begun at 10:15. 11:10: Surgical dissection was begun around the heart. 11:21: Right pulmonary artery was ligated. 11:57: Pericardium was opened. 12:01: A massive hemorrhage occurred from the lung hilus. 12:13: Bleeding still continuing and during a period of six to eight minutes 500 c.c. of blood had been replaced. By 12:23 a total of 3,000 c.c. of blood had been given by syringe. The hemorrhage continued and at 12:30 the heart stopped and the pressure began dropping to 23 mm of mercury

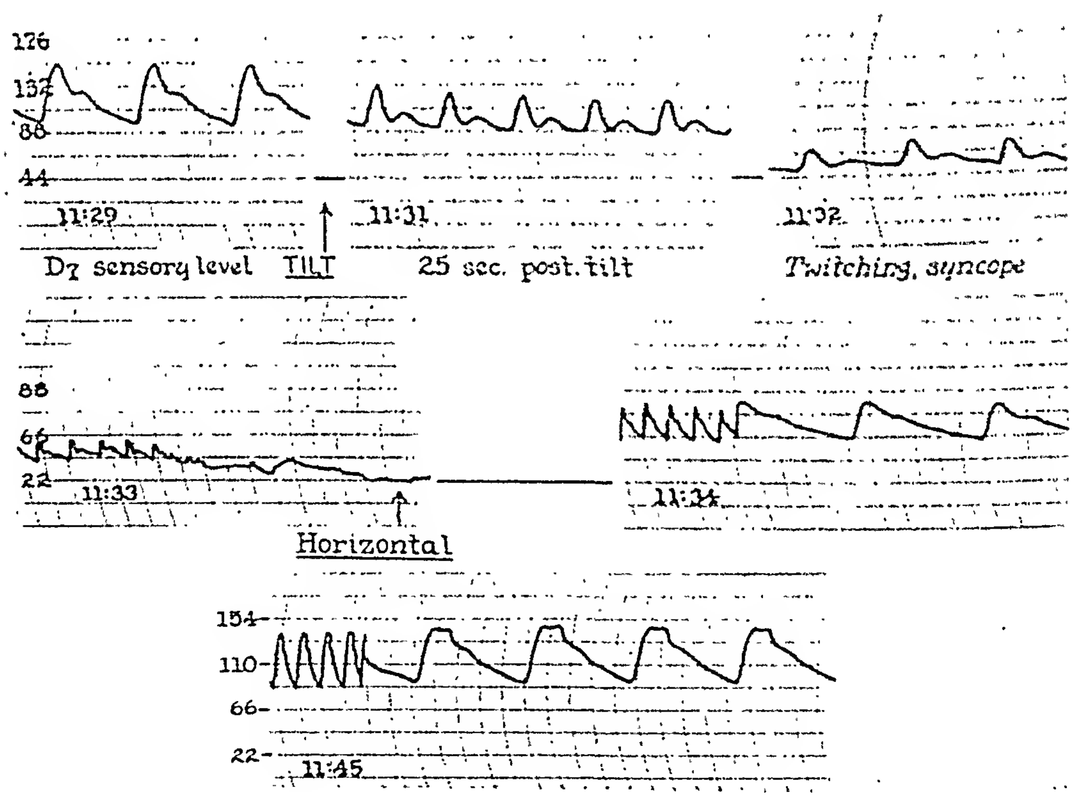

Fig. 9.—Brachial artery pressures from a 42-year-old man under conditions described in text. 11:29 shows the pretilt tracings with abolition of pin prick sensation at D-7. The subject was tilted to the 70° head-up position and the 11:31 record was obtained twenty-five seconds later. The subject became dizzy and at 11:32 twitching with syncope appeared. The pressure continued to fall and at 11:33 distinct beats were not visible in the arterial tracing. The subject was returned immediately to the horizontal position with a return of pulsation and pressure as shown at 11:34. There was abolition of sensation to D-7 from 11:34 through 11:45.

DISCUSSION

With the method of recording described in this paper, one can transcribe detailed notes directly under the arterial pressure tracings as the paper unrolls from the ink-writer. The elimination of the time lost in developing photographic records makes it possible to correlate cause and effect relationships more accurately and to avoid delay in the application of therapeutic measures if the apparatus is being used under clinical conditions. The method has the further advantage that records can be obtained at a distance of twenty feet from the patient with no other connection to the recording unit than three small flexible conductors. Such recording has been continued for over ten hours and then stopped voluntarily. The method imposes no discomfort on the subject. The equipment can be transferred readily from room to room and from patient to patient. The entire procedure can be maintained under sterile conditions. Records can be taken in the erect, supine, and lateral positions, all awkward positions for recording with the hypodermic manometer. The apparatus can be used under clinical conditions with no disruption of routine. There is relatively little limitation of an investigation imposed by motion of the subject since the catheter can be better maintained in position than a rigid needle. Finally, the Riva-Rocci method of measuring systolic and diastolic pressures is inaccurate under certain conditions.[9,10] A knowledge of the pressures developed with each heart beat, therefore, may often be of great value.

The proposition that pulse pressure patterns indicate changes in the hemodynamics is not new, and for years Wiggers and others have stressed the utility of such curves.[5,10] It is well known that changes in peripheral resistance will produce a different type of alteration in the arterial pulse from the alteration due to changes in stroke volume. Inability to assess the influence on pressure pulse curves of variables such as the elasticity of the blood vessels and the viscosity of the blood have made some workers hesitant in their use. If each record is used as its own control, however, these variables are less significant since they are usually constant enough to be neglected in the interpretation of such gross changes as have been shown in this paper.

SUMMARY

1. A method for recording arterial pressure pulse waves in man is presented which has certain practical advantages over techniques in current use.

2. Cases are presented to demonstrate the utility of such an apparatus.

3. The application of this method to experimental and clinical procedures provides the observer with an opportunity of investigating large numbers of subjects under a wide range of conditions.[12,13]

The authors wish to thank Dr. H. C. Bazett for advice in the preparation of this paper and Dr. P. R. Dumke, Dr. K. F. Eather, and Dr. L. Wiley for aid in collection of the clinical data.

ADDENDUM

Since the earlier work reported in this paper was completed, the Moore School of Electrical Engineering has developed an improved amplifier system for use with this procedure. This amplifier has been used in recent work with distinct advantage through improvements in stability and linearity over a wider range and through the greater convenience which it affords. A description of this design appears in the paper which follows. (Tompkins, Howard E.: A New Capacitance-Blood-Pressure-Manometer Amplifier).

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A NEW CAPACITANCE-BLOOD-PRESSURE-MANOMETER AMPLIFIER

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IN THIS paper a new amplifier circuit for use with the Lilly capacitive-type manometer[1] for the measurement of intra-arterial blood pressure is described, and performance data taken with the pilot model are given. The physiological uses of this type of equipment have been described in the preceding paper.[2]

This amplifier, used with a Lilly manometer, will measure from 0 to 370 mm. Hg in five ranges, each range normally starting from 0 but with simple provision for extending each range down to 15 mm. Hg below atmospheric pressure. At maximum sensitivity, 27 mm. Hg gives full scale deflection. The linearity on each range is ±3 per cent, as shown in Figs. 1 and 2.

The stability of the electrical system is good, as is partially shown in Fig. 3, and the stability of the over-all system tends to be limited by the manometer head rather than the amplifier. Stability with respect to manipulation of the connecting cable between the patient and the amplifier is excellent, being less than the effect of 1 mm. Hg pressure. The equipment may readily be used at distances of the order of twenty feet from the patient, or at longer distances with a special cable.

The necessary bandwidth for accurate representation of blood pulse wave forms extends from 0 (direct current) to at least 70 cycles per second.

The capacitance of the Lilly manometer will change 6 micromicrofarads from an initial 125 micromicrofarads under an applied hydrostatic pressure of 300 mm. of mercury. This change requires an extremely small volume of fluid; hence the inertia of the liquid system is small, and the capacitance is able to follow pulse wave variations of from 0 to 70 cycles per second or well over 100 cycles *per second, depending on the catheter used. A study of the precise bandwidth* of such fluid systems is in progress.

The output of the amplifying system must be presented in a clear, permanent form, so that the record of the pulse and average pressure may be studied after the actual measurement (or operation) is concluded. For clinical use, however, the record must also be immediately visible during the measurement. An ink-writing galvanometer is the most convenient instrument on which to present the information.

Alternatively, a conventional mirror galvanometer using photographic recording may be used. In this case the pulse wave form can be observed on a good medium-persistence cathode-ray oscillograph, and the average blood pressure may be observed instantaneously with a direct current milliammeter. This set-up is considerably more clumsy than the ink-writer.

The circuit described herein, which is being produced commercially,* in slightly modified form, is designed specifically to drive an ink-writer,† but will

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From the Moore School of Electrical Engineering, University of Pennsylvania.
Received for publication March 29, 1948.

*By Technitrol Engineering Co., 3212 Market Street, Philadelphia 4, Pa.

†Such as Model BL-201 or BL-202 Oscillographs manufactured by the Brush Development Co., 3405 Perkins Ave., Cleveland 14, Ohio.

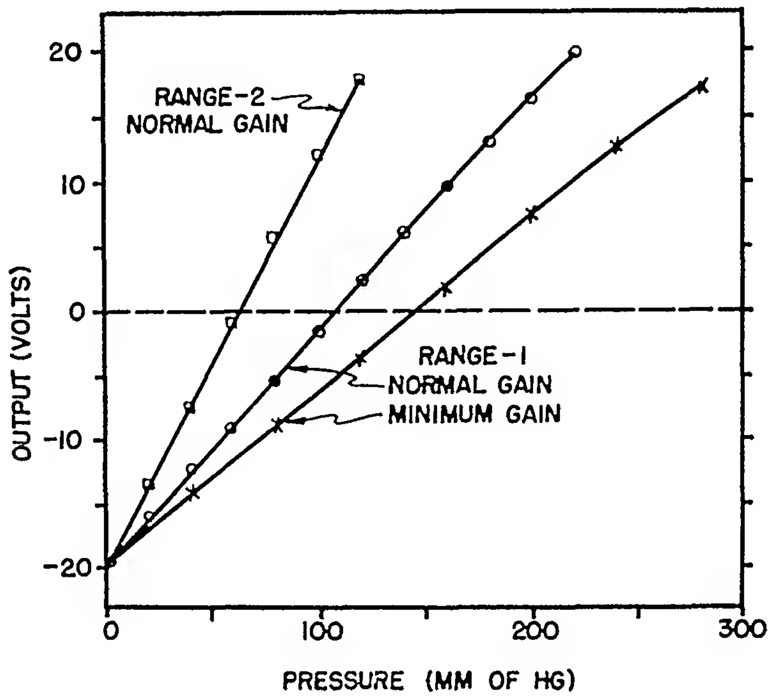

Fig. 1.—Deflection of 1,500 ohm ink-writing galvanometer versus pressure at Lilly manometer head for Ranges 1 and 2 at normal gain and Range 1 at minimum gain. One volt corresponds to a galvanometer deflection of 1.05 millimeter.

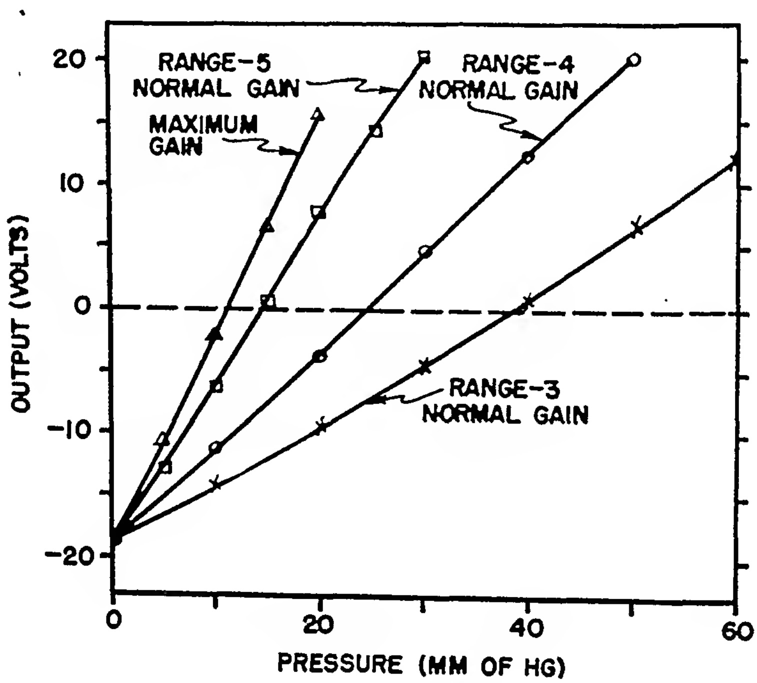

Fig. 2.—Deflection of 1,500 ohm ink-writing galvanometer versus pressure at Lilly manometer head for Ranges 3, 4, and 5 at normal gain and Range 5 at maximum gain. One volt corresponds to a galvanometer deflection of 1.05 millimeter.

also drive any other common type of indicating instrument. The bandwidth of the electrical system using the ink-writer is shown in Fig. 4.

This particular circuit is not the only one that has been used with capacitance blood pressure manometers. Other systems have been described and built by Skouby and others[3,4] in Denmark.

The circuit is applicable to any measurement problem in which the desired information can be observed as a capacitance variation. Output versus capacitance change is shown in Fig. 5. Other medical and nonmedical uses for the equipment should, therefore, develop.

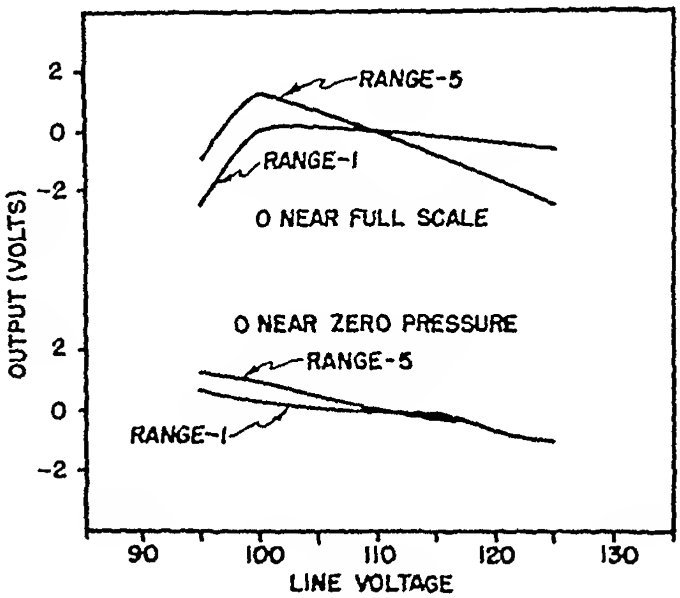

Fig. 3.—Variation of zero reading and a reading near full scale on Ranges 1 and 5 versus 60 cycle line voltage applied to unit.

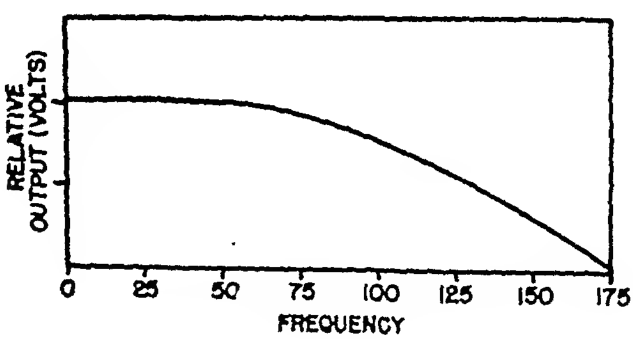

Fig. 4.—Frequency response of electrical system from radio frequency bridge through ink-writing galvanometer. *The falling high frequency response of the galvanometer is compensated for by the amplifier.*

A block diagram of the system is shown in Fig. 6 and a detailed schematic representation in Fig. 7. The capacitive manometer head is part of one arm of an alternating current bridge which, although adjusted for exact resistive balance, is slightly unbalanced reactively. When the blood pressure varies, the

capacitance of the manometer head varies, and the reactive unbalance of the bridge is increased, thus increasing the transmission of the bridge.

A radio frequency (2.2 megacycles) constant amplitude oscillator drives the input of the bridge. The output voltage of the bridge is thus proportional to the unbalance caused by the blood pressure. This voltage, still a radio frequency alternating wave, is then amplified by a two-stage tuned amplifier, shown on the block diagram as the R. F. Amplifier. Any convenient frequency may be used. The choice of 2.2 megacycles was dictated by the capacitance of the manometer head and the available space for a coil to resonate it.

The amplified radio frequency signal is detected by a vacuum diode (part of the 6AT6 tube) and the resulting pulsating direct voltage is a replica of the instantaneous blood pressure at the manometer head. This voltage is amplified in the two-stage direct coupled amplifier to a power level sufficient to drive the recording galvanometer.

The output circuit, in the cathode of the 6AQ5 tube, is designed to drive a 1,500 ohm ink-writer, whose rest position is at mid-scale. Accordingly, the output voltage can vary from 23 volts negative to 23 volts positive about ground (or chassis), when a 1,500 ohm load is connected at Output 1. Alternatively a low impedance galvanometer may be used at Output 2 (see Fig. 2). By appropriate adjustment of the zero-set control, the amplifier can be used with an indicating instrument, the rest position of which is at zero pressure, that is, at one end of the instrument scale.

The output circuit saturates immediately beyond the stated output power and the output voltage will not keep rising. This feature protects the indicating instrument from damage. It is essential that some such protection be provided in a circuit of this type, for without it the indicating instrument would be overloaded severely if the manometer head were disconnected or if the zero set knob were twisted inadvertently.

The range control switch in the radio frequency amplifier provides five different pressure sensitivities, which at normal gain control setting require 35, 60, 90, 160, and 270 mm. Hg pressure, respectively, for full scale (5.0 cm.) deflection (a total voltage swing of about 46 volts). The gain control in the detector circuit will increase or decrease the sensitivity of each range about 1.4 to 1; thus, it provides any desired intermediate sensitivity between ranges and extends Range 1 up to 370 mm. Hg full scale and Range 5 down to 27 mm. Hg, full scale.

By adjustment of the zero set control the bottom of the scale on each range can be set anywhere from −15 mm. Hg (that is, below atmospheric pressure) to approximately one-half full pressure for that range. This allows expansion of a pulse wave if desired, and extends the range of the instrument to slightly higher pressures.

In all, only three controls are used in operating the instrument: the range, gain, and zero set controls. Bridge alignment, which should be checked every few weeks, requires the adjustment of four controls which are available at the side of and inside the case. A simple check on bridge alignment is possible from the front panel as the zero will shift from range to range if the bridge is not aligned correctly for the particular manometer head being used.

The stable performance of this circuit is due largely to the following factors:

1. A small coil is mounted in the manometer head, and is connected in a series between the head capacitance and the coaxial transmission line leading back to the main chassis. The inductance of this coil resonates with the head capacitance at the radio frequency being used (2.2 megacycles). Thus, the coaxial transmission line connecting the patient with the equipment is at low impedance (about 20 ohms) and variations in its capacitance have very little effect on the output.

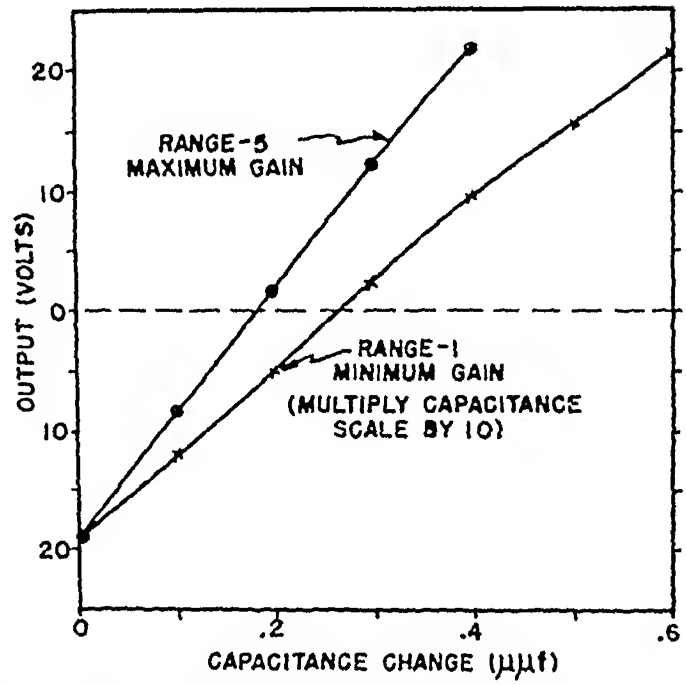

Fig. 5.—Deflection of 1,500 ohm ink-writing galvanometer versus capacitance change at input on Ranges 1 and 5 at extreme gains. Note different scales.

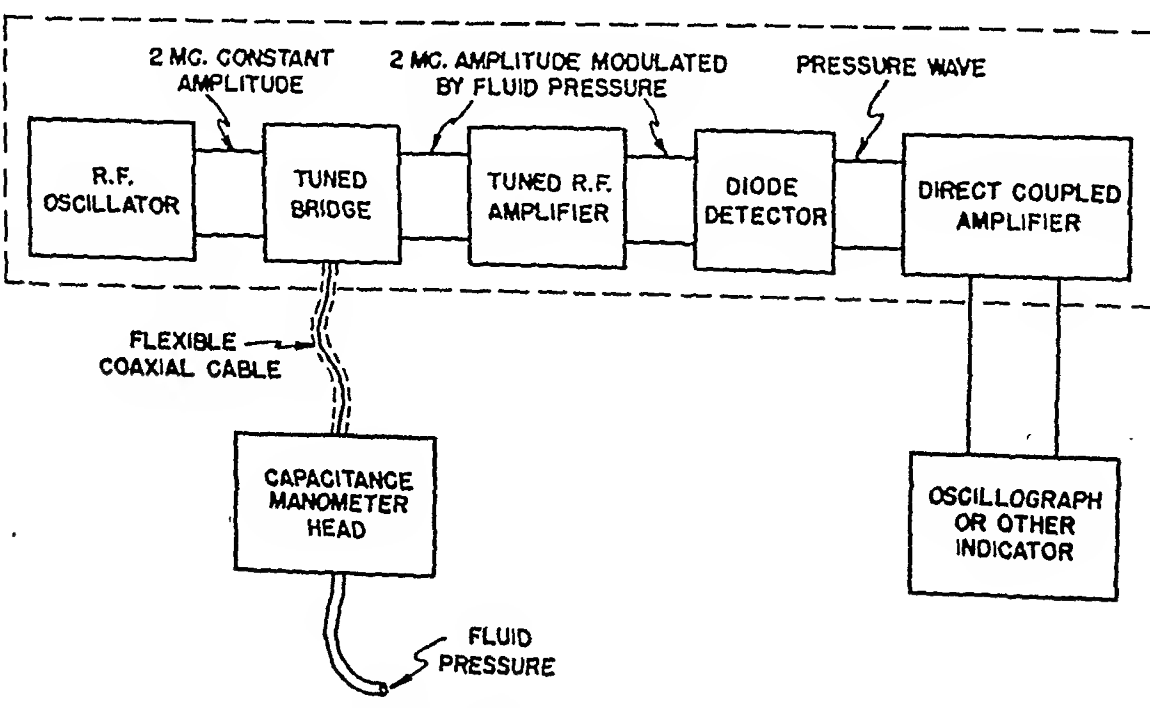

Fig. 6.—Block diagram of manometer amplifier system.

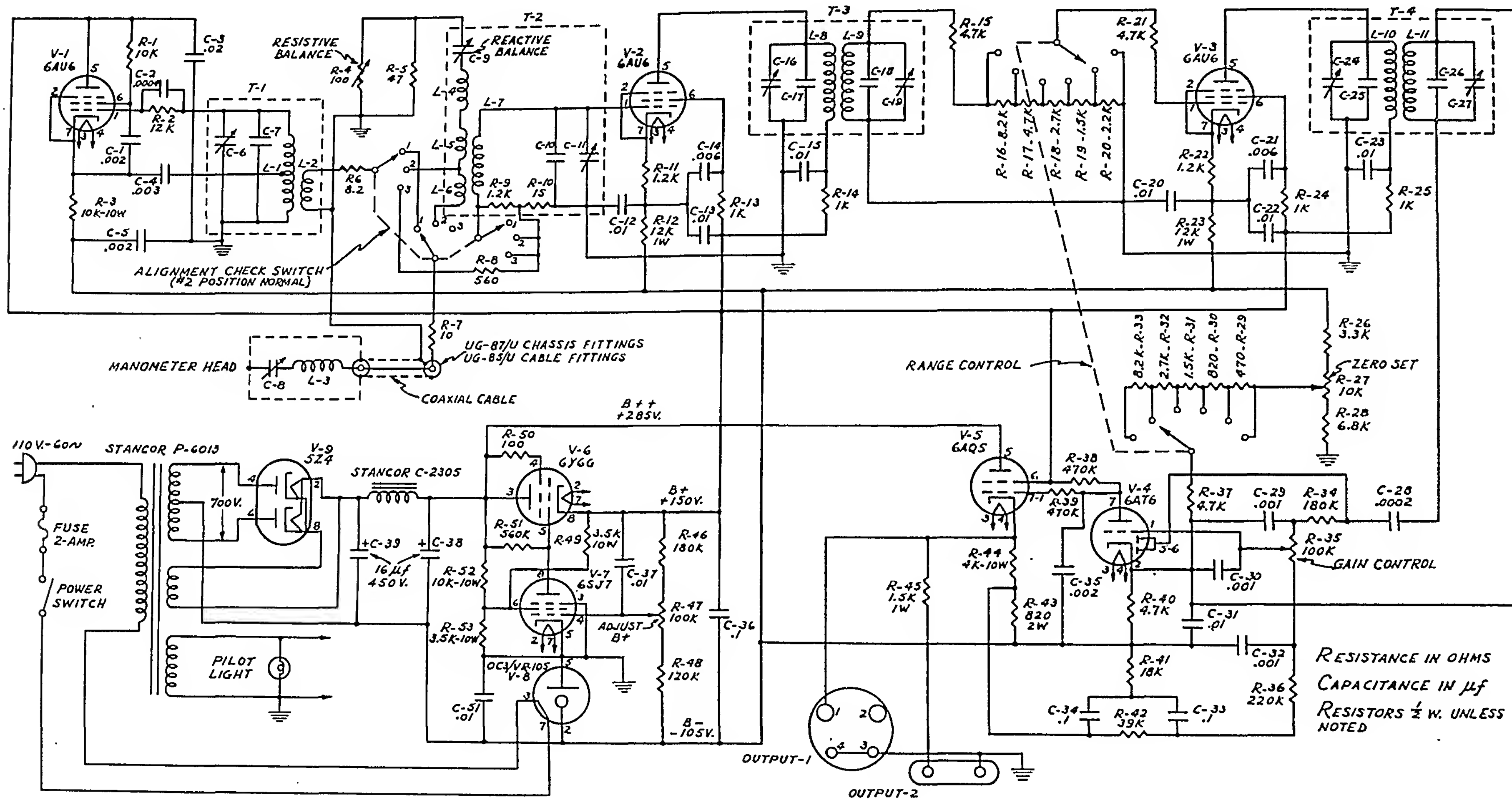

Fig. 7.—Schematic diagram of capacitance-blood-pressure-manometer amplifier. *T-1* is a 2.2 megacycle oscillator tank circuit with an 8 ohm output winding. Oscillator output is 0.7 volts at the output winding. *T-2* is the radio frequency bridge transformer. Windings *L-5* and *L-6* are four turns each, balanced 1/16 inch from tuned secondary winding *L-9*. Coil *L-4* and its trimming capacitor *C-9* are tuned to 2.2 megacycles and form the major part of one arm of the bridge. *T-3* and *T-4* are conventional critically coupled interstage transformers. The manometer head (*L-3* and *C-8*) is tuned to 2.2 megacycles. Alignment check switch is normally in Position 2 during use. Position 1 is used in aligning the oscillator to the frequency of the head. Position 3 is used in checking the circuit in the absence of a manometer head. For production, the detail of this circuit has been modified by the Technitrol Engineering Co.

2. The use of a radio frequency amplifier system obviates the need for a high-gain direct-coupled amplifier, which would inevitably introduce a great deal of instability. The only direct-coupled amplifier used in this unit is for power amplification at the output, and this two-stage amplifier has a net voltage gain of less than 6. The rest of the available direct-coupled amplifier gain is used to provide inverse feedback for increased stability.

3. Inverse feedback of the signal is used in all the amplifier circuits so that their performance will be relatively independent of tube age and operating conditions.

4. Direct current degeneration is used in both oscillator and radio frequency amplifier circuits to provide stable tube operating points which are relatively independent of heater voltage and tube age.

5. An electronically regulated power supply is used which provides relative freedom from the effects of varying power line voltage over a range from 95 to 130 volts (Fig. 3).

Of course, stability requires, in addition, that all components be operated well within their ratings, and that good quality components be used. For example, only air padders should be used in the tuned circuits of the amplifier.

ACKNOWLEDGMENT

The design of this circuit is based in large part on an earlier version by Mr. Theodore H. Bonn. The author's thanks are due to Dr. H. C. Bazett of the Physiology Department of the University of Pennsylvania for his support and encouragement, and to Mr. L. H. Peterson of the same department for his able presentation of the medical man's point of view toward this device.

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ELECTROCARDIOGRAPHIC CHANGES FOLLOWING ELECTRO-SHOCK THERAPY IN CURARIZED PATIENTS

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THE therapeutic benefit of electrically induced convulsions in certain neuropsychiatric disorders has in recent years become firmly established. Many of the candidates for this form of treatment are in the middle and older age groups, and the problem is frequently complicated by coexisting cardiovascular disease. The decision regarding what clinical and electrocardiographic abnormalities contraindicate electroshock therapy in such patients is difficult, since there is inadequate knowledge regarding methods of prevention of alarming reactions and mechanisms of fatal outcome. Acute myocardial infarction and aneurysms are usually considered absolute contraindications to electroshock therapy. Yet we are aware of one acutely suicidal patient of Dr. Titus Harris[1] who had an acute myocardial infarction and survived electroshock therapy. He has also treated without difficulty a patient with a severe, agitated depression who had a large thoracic aneurysm. Although it is generally agreed that cardiovascular disease adds to the risk of therapy, the indications for treatment may be so urgent that they outweigh this increased risk.

Reported fatalities are relatively rare, and were reviewed by Ebaugh and associates[2] and more recently by Will, Rehfeldt, and Neumann.[3] The latter authors collected records of thirty-three deaths from electroshock in the American and English literature, fifteen of which occurred immediately or shortly after the application of the electrical stimulus. The causes of the sudden deaths remain obscure, since clinical descriptions of the respiratory and cardiac systems are not conclusive, and an electrocardiogram has never been taken during exitus in such situations. The pathology found at post-mortem examinations is usually not adequate to explain the cause of death. Kalinowsky and Hoch[4] believe that most fatalities are cardiovascular in origin, although respiratory complications are more common.

Curarization before treatment is frequently a routine procedure, its purpose being to decrease the severity of the convulsions and to lessen the increased

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cardiac burden imposed by the violent muscular exercise. Several investigators believe that the pretreatment use of this drug leads to additional dangers, and we have had knowledge of one death from curarization alone. Lowinger and Huddleston[5] suggested that curare played an important role in the causation of marked variability in blood pressure, pulse, and respiration noted in curare-preceded electrical convulsions. Woolley[6] was able to abolish these with adrenalin or Prostigmine. Jones and Pleasants[7] have advised the cautious use of curare in patients with severe cardiac disease, believing that the period of apnea after the convulsion is thereby prolonged to aggregate myocardial ischemia from sclerotic vessels. In a report of a series of twenty-one cardiac and noncardiac patients studied here, no electrocardiographic changes were found after curarization,[8] but this does not absolve curare as a contributing factor. Intravenous Prostigmine is usually given for respiratory difficulty following the convulsion, in an attempt to counteract the aggravation of anoxia caused by curare-induced muscular weakness.

In 1941, Bellet, Kershbaum, and Furst[9] reported an electrocardiographic study during and after sixty-five electrically induced major seizures and thirty-five minor seizures in fifty patients with normal cardiovascular systems. Changes were noted as being less frequent and less severe than those that had been observed in Metrazol therapy and in insulin shock therapy. Following the convulsion there was frequently a slowing of rate which was considered to be vagal in origin and which, in three cases, was abolished by atropine. In one patient given curare before the electrical stimulus, idioventricular rhythm followed the convulsion, but it was absent after a later treatment in which curare was omitted. Kline and Fetterman[10] in 1942 summarized studies of Lead II and in some cases a single apical lead immediately after the electroshock convulsion in forty-two psychotic patients. Cardiac arrhythmias were not conspicuous, and an elevated T wave was noted in all but eight cases. Five patients with cardiovascular disease showed no unusual changes. In 1943, Nyman and Silfverskiöld[11] took electrocardiograms immediately after electroshock convulsions in thirteen patients. They found a rise in P_2 and T_2 and a fall in R_1. On the basis of similarity of these changes to changes after the Valsalva maneuver, these investigators considered the mechanism in the two conditions to be the same. Altschule, Sulzbach, and Tillotson[12] recorded electrocardiograms before and after thirty seizures in ten patients, noting frequent arrhythmias of apparent vagal origin. The uniform increase in height of P waves was attributed to dilatation of the atria after the convulsion, and alterations in the ventricular complexes were not considered significant. Evans[13] observed transient changes apparently indicating improvement in the electrocardiograms of five patients with heart disease following electroshock. These changes consisted mainly in reversal of negativity or increase in height of T waves.

The present study of the effects of electroshock upon the electrocardiogram in curarized patients was stimulated by observation of several alarming post-treatment reactions and two deaths which immediately followed treatment and apparently were due to cardiac arrest. These two fatalities have been reported in detail[14] and occurred immediately after the initial treatment in a 16-year-old

Mexican girl and after the seventh convulsion in a 70-year-old white woman. Unfortunately, no tracings were taken during exitus, but the pretreatment electrocardiograms are shown in Fig. 1.

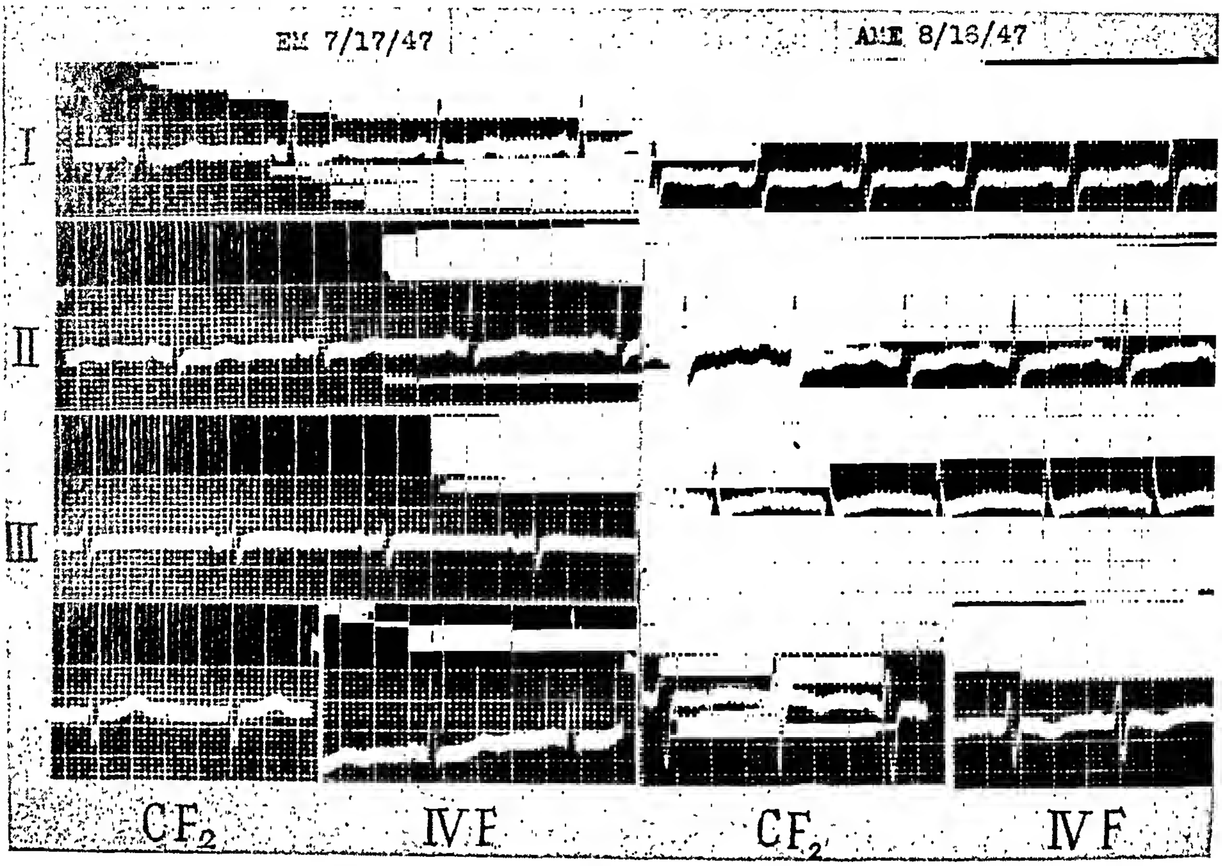

Fig. 1.—Electrocardiograms before treatment of two patients with fatal reactions after electroshock. E. M., a 70-year-old white woman, expired immediately after the seventh treatment. The Q-T interval is 0.40 second, the upper normal for the rate of 70 per minute. A. M. E., a 16-year-old Mexican girl, expired after the first electroshock convulsion, from apparent cardiac arrest. The P-R interval is 0.22 second, and the rate is 94 per minute. The T wave is flat in Lead 1, low in Leads II and III, and negative in Lead CF_2 and IVF.

CLINICAL MATERIAL STUDIED AND METHODS USED

The cardiovascular status of each patient was evaluated by means of a painstaking history, complete physical examination, and electrocardiogram with routine chest leads (CF_2 and CF_4). Curarization was than accomplished before each treatment with d-tubocurarine chloride given intravenously at a rate of 1.0 c.c. per minute. The dosage was 0.05 c.c. (1 unit) per kilogram of body weight less a safety factor of 0.5 to 1.0 c.c., depending on the degree of relaxation achieved. A base-line tracing consisting of all three limb leads was taken with a Sanborn Viso-Cardiette, a rugged, direct-writing electrocardiograph, after completion of curarization and immediately preceding the application of the electrical stimulus with the Electra conventional stimulator. The limb leads were left in place and as much of a continuous tracing in Lead II as possible was taken during the tonic and clonic phases of the convulsion. Immediately after the

convulsive movements ceased, beginning with Lead II, a continuous tracing with all three limb leads was recorded as long as rapid changes were taking place. Then intermittent tracings were taken at brief intervals until the electrocardiogram had returned to its pretreatment form, usually five to ten minutes after the convulsion. In a few of the patients with postconvulsive respiratory difficulty, 1.0 c.c. of 1:2,000 Prostigmine methylsulfate was given intravenously after one to two minutes of tracings had been obtained.

Using this procedure, a series of 304 tracings was obtained before, during, and after major convulsions in 126 consecutive curarized patients. In twenty-three instances tracings were also taken during preliminary petit mal reactions in these patients. No deaths were encountered. A summary of the age and sex of the patients, with the number of electrocardiograms taken, is given in Table I. The psychiatric diagnoses were: psychotic depression, 70; manic, 5; schizophrenia, 32; others, 19.

TABLE I. *AGE AND SEX DISTRIBUTION OF CLINICAL MATERIAL*

	10-19	20-29	30-39	40-49	50-59	60-69	70-79	TOTAL
Male patients	1	3	7	14	8	4	2	39
Electrocardiograms	2	11	12	28	25	7	4	89
Female patients	2	10	21	21	23	8	2	87
Electrocardiograms	5	29	42	51	62	22	4	215
Number patients								126
Number electrocardiograms								304

DETAILS OF THE ELECTROCARDIOGRAPHIC FINDINGS

Satisfactory electrocardiograms were recorded during the tonic phase in fifty-one major convulsions in thirty-six patients, and in three instances the entire tonic and clonic portions were obtained. Excerpts from one of these records are shown in Fig. 2. Immediately following the stimulus, all such tracings showed a gradually increasing sinus tachycardia, which reached a rate at the end of the tonic phase averaging 35 per minute over the beginning value. Single premature ventricular contractions were observed during the tonic portion of the convulsion in three cases, and in one there was transient atrial fibrillation. Twenty-three petit mal episodes were also recorded, four patients having two such successive reactions and two having three. In each instance increasingly stronger electrical stimuli were applied until a major convulsion was finally produced. Ten of the petit mal reactions were accompanied by decreases in sinus rate varying from 5 to 50 per minute, seven by no rate change, and six by increases of 5 to 30 beats per minute.

An analysis of the patients showing clinical or electrocardiographic evidence of heart disease is presented in Table II. It seemed desirable to compare the changes of rhythm noted in this series of tracings with the changes observed in patients with apparently normal hearts, since such comparisons had not been

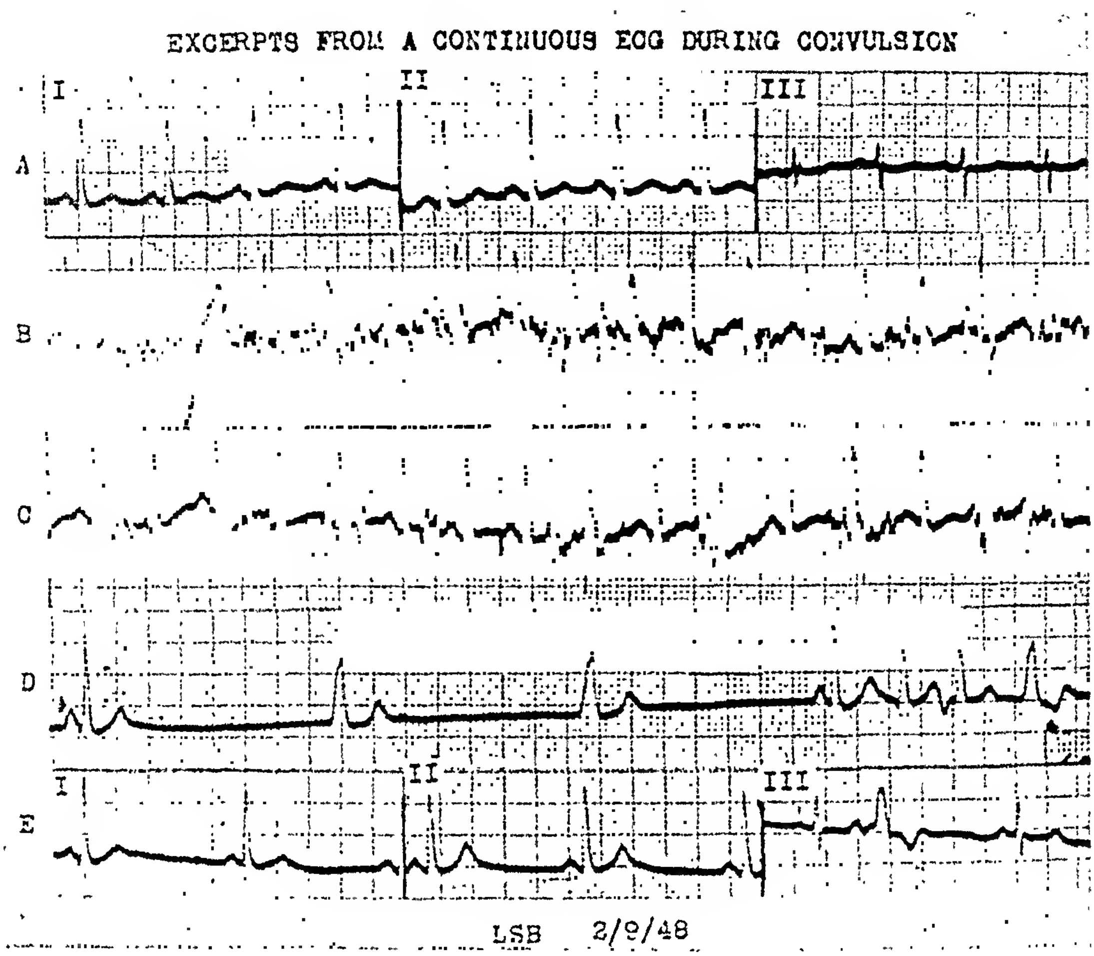

Fig. 2.—Excerpts from a continuous tracing made during and after major convulsion in L. S. B., a 55-year-old white man with no evidence of heart disease. *A*, Limb Leads I, II, and III before the electrical stimulus. *B*, Lead II during the tonic phase, showing premature ventricular contraction. *C*, Clonic phase, with rapid sinus tachycardia. *D*, Lead II immediately after the end of the convulsion; temporary suppression of sinus pacemaker with impulses initiated in A-V bundle, followed by short run of ectopic atrial impulses. *E*, Limb Leads I, II, and III one minute later with T-wave elevation in each. Tracing taken five minutes later showed a form similar to that shown in *A*.

TABLE II. ANALYSIS OF PATIENTS WITH HEART DISEASE

	NO. PATIENTS	NO. ECG
Definite ECG evidence of myocardial damage	7	20
ECG suggestive of damage with positive clinical signs of heart disease	15	37
ECG negative, with clinical evidence of heart disease	4	13
Total	26	70

made previously. In the pretreatment electrocardiograms, there were occasional premature ventricular contractions in two patients with heart disease and in one patient with a normal heart. Nodal ectopic beats occurred in the base-line tracing of one patient with heart disease. Table III shows a summary of all the disorders of rhythm, these generally beginning immediately after the last con-

vulsive twitch and being completed within five minutes. Illustrative electrocardiograms showing some of the more striking changes are included in Figs. 3, 4, and 5.

TABLE III. ARRHYTHMIAS FOLLOWING 304 MAJOR CONVULSIONS AFTER ELECTROSHOCK

	CV DISEASE 70 ECG		NO CV DISEASE 234 ECG		TOTAL 304 ECG	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Sinus arrhythmia	8	11.4	27	11.5	35	11.5
Ectopic beats, atrial	33	47.1	56	19.7	89	26.0
Ectopic beats, ventricular	28	40.0	29	12.4	57	18.7
Ectopic beats, nodal	5	7.1	13	5.5	18	5.9
Wandering pacemaker	23	32.9	23	9.8	46	15.1
Nodal rhythm	16	22.9	28	12.0	44	14.5
Transient S-A standstill	0	0	6	2.6	6	2.0
Blocked S-A impulses	8	11.4	4	1.7	12	3.9
Prolonged P-R interval	7	10.0	7	3.0	14	4.6
Wenckebach phenomenon	0	0	2	.9	2	.7
2:1 A-V block	0	0	2	.9	2	.7
Parox. atrial tachycardia	1	1.4	1	.4	2	.7
Atrial fibrillation	0	0	1	.4	1	.3
Idioventricular rhythm	0	0	2	.9	2	.7
Ventricular tachycardia	0	0	1	.4	1	.3
Bigeminy (vent. pre. con.)	3	4.3	0	0	3	1.0
Trigeminy (vent. pre. con.)	0	0	1	.4	1	.3
Number of Above Arrhythmias in Each ECG						
No rhythm disturbance	13	18.6	108	46.1	121	40.0
One rhythm disturbance	21	30.0	73	31.2	94	30.9
Two disturbances	19	27.1	33	14.1	52	17.1
Three or over	17	24.3	20	8.5	30	9.9
Tachycardia and Bradycardia						
Sinus tachycardia over 135 per minute	31	44.3	123	52.6	154	50.7
Sinus bradycardia less than 60 per minute	1	1.4	20	8.5	21	6.9
Both sinus tachy. and brady. in same ECG	0	0	5	2.1	5	1.6

The T-Wave Changes.—In Table IV are summarized the changes in the P waves, RS-T segments, and T waves after the convulsive episodes. No significant difference was observed in this regard between patients with heart disease and patients with normal hearts. There were changes of the type usually accepted as evidence of improvement in thirteen electrocardiograms of eleven patients showing suggestive or definite electrocardiographic evidence of myocardial damage before the convulsion. These changes consisted in higher T waves in Leads I and II in five instances and in all limb leads in the other eight tracings.

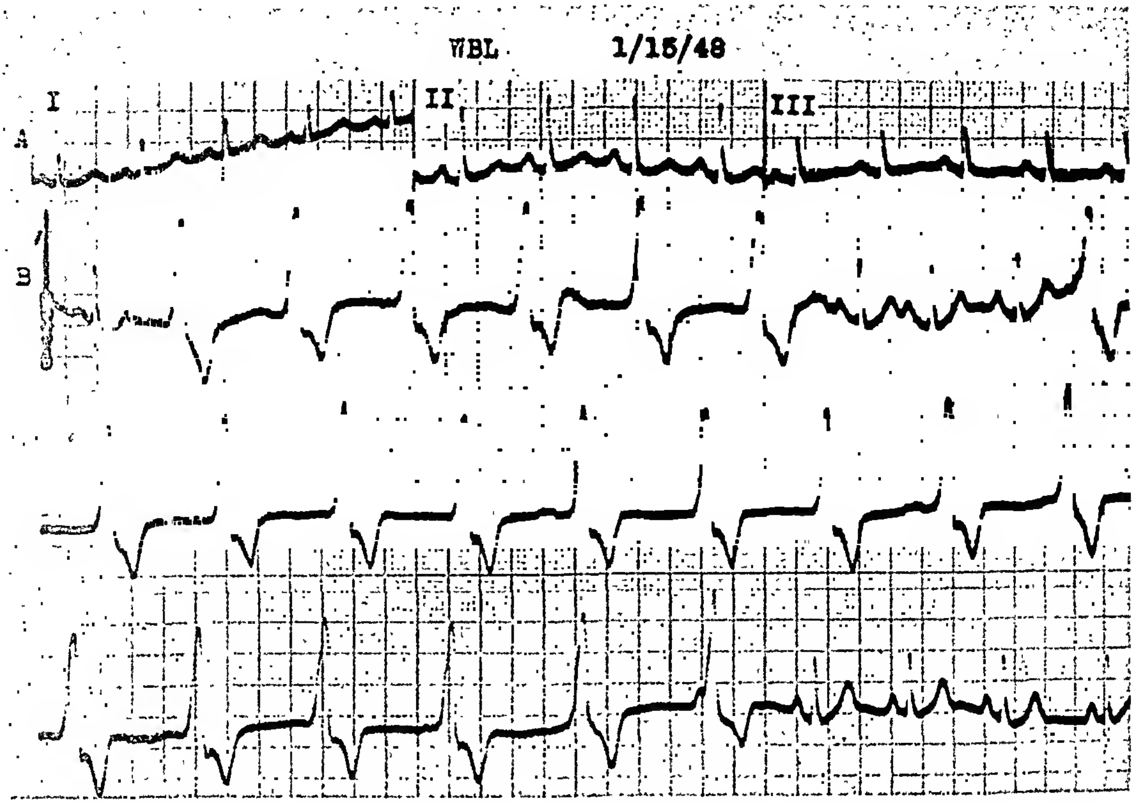

Fig. 3.—*A*, Pretreatment limb leads I, II, and III. *B*, Lead II following convulsion in W. B. L., a 54-year-old white woman without evidence of heart disease. Note the runs of idioventricular rhythm at the rate of 78 per minute, with retrograde P waves. T_2 is elevated and $RS\text{-}T_2$ is slightly depressed in the portion showing sinus rhythm.

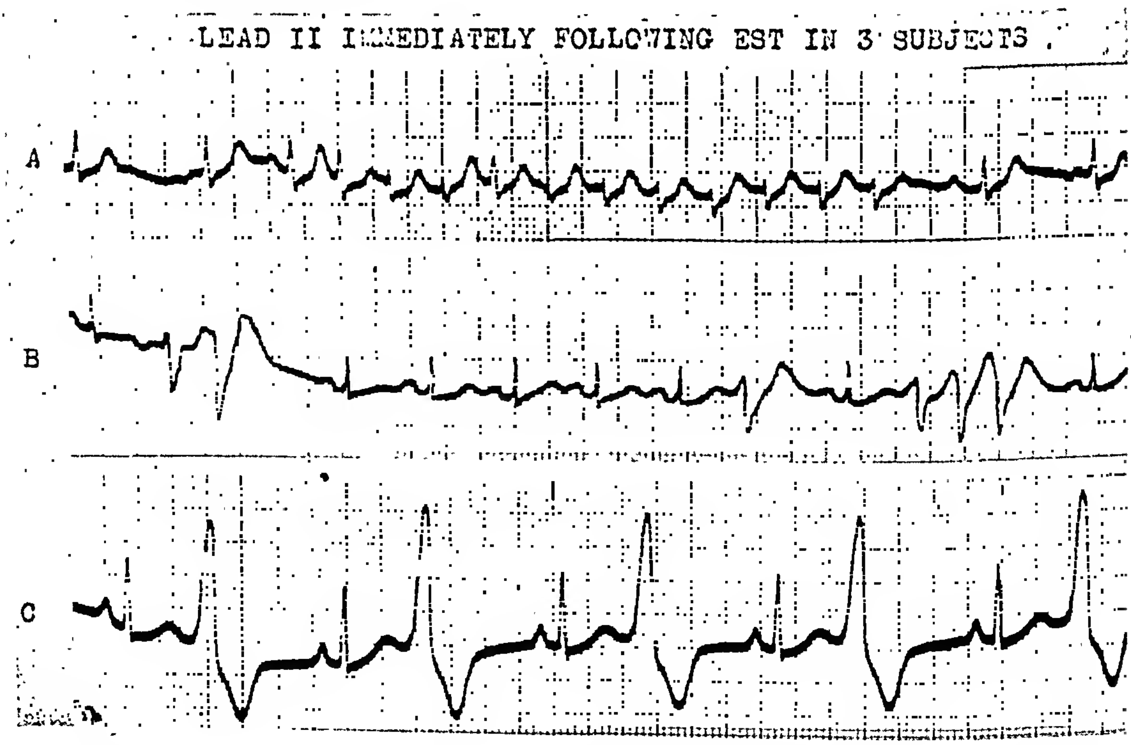

Fig. 4.—Lead II in three subjects immediately following electroshock therapy. *A*, Brief episode of paroxysmal atrial tachycardia in moderately hypertensive 67-year-old white woman with suggestive electrocardiographic signs of myocardial damage. *B*, Ventricular ectopic beats in rapid runs of two and three in a 50-year-old white woman with no evidence of heart disease. Marked respiratory difficulty and cyanosis followed the convulsion, and inhalation of pure oxygen seemed to clear up the premature contractions. *C*, Bigeminy with ventricular premature contractions in a 48-year-old white woman with blood pressure 184/120 and suggestive electrocardiographic evidence of myocardial damage. This was prevented in later convulsions with quinidine sulfate, orally.

The alterations were only temporary, since the T waves had decreased to the original voltage in five minutes. Fig. 6 is presented as an example of such increase in height of T waves in a patient with no heart disease.

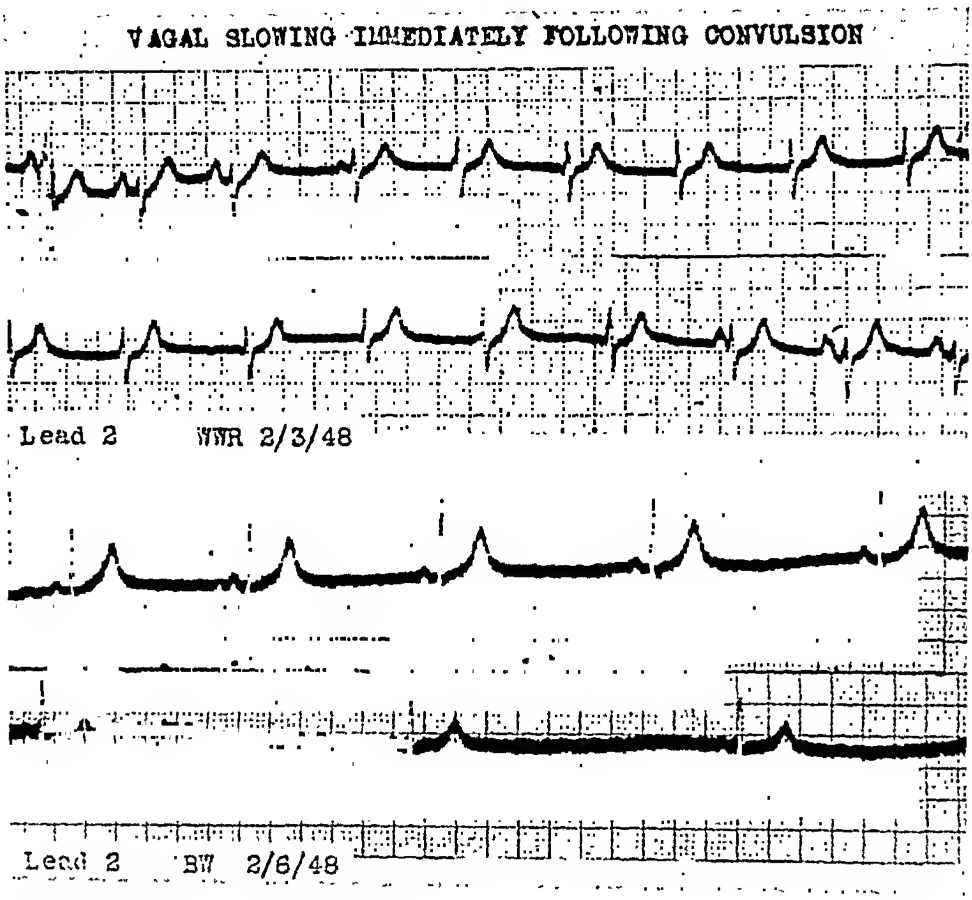

Fig. 5.—W. W. R., a 41-year-old white man with no evidence of heart disease. Tracing shows displacement of pacemaker to A-V node and its return. B. W., a 43-year-old white woman with no heart disease. Convulsion is followed by marked sinus bradycardia, rate 25 per minute.

TABLE IV. CHANGES IN P WAVE, RS-T SEGMENT, AND T WAVE IN 304 ELECTROCARDIOGRAMS AFTER MAJOR CONVULSIONS IN ELECTROSHOCK THERAPY

	LEAD I		LEAD II		LEAD III	
P wave	Higher	21	Higher	154	Higher	116
RS-T segment	Depressed	68	Depressed	212	Depressed Elevated	106 1
T wave	Higher Lower	158 2	Higher Lower	192 2	Higher Negative	156 1
No changes in RS-T and T	127		36		90	

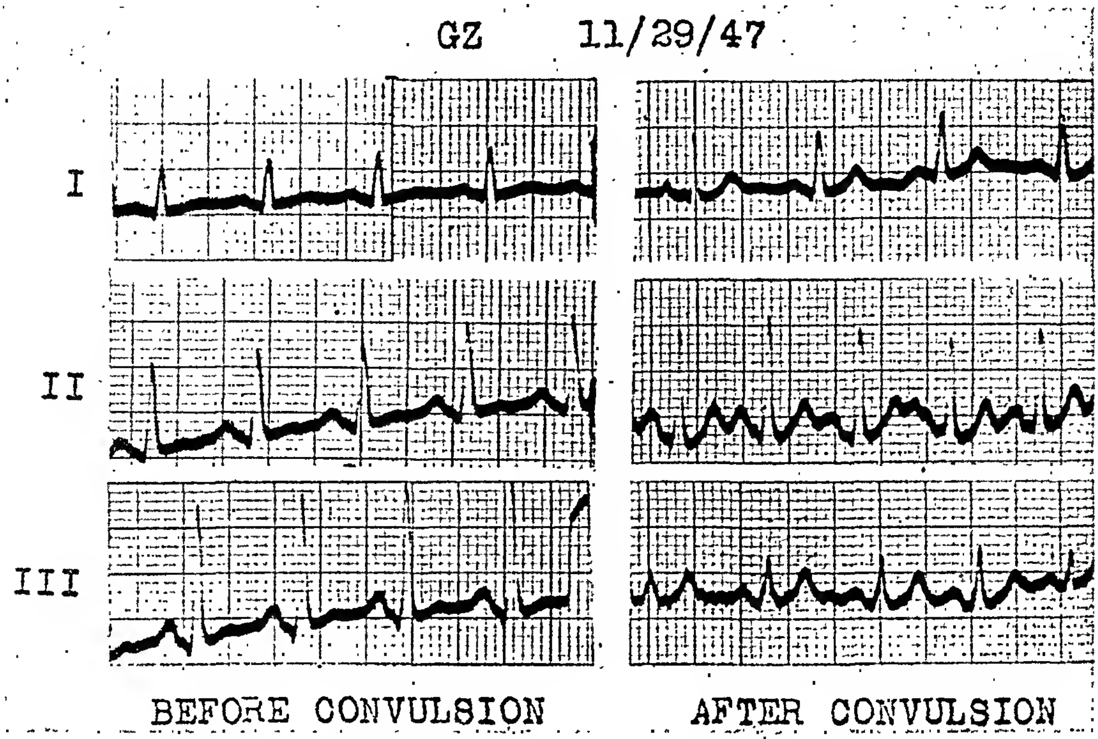

Fig. 6.—Limb leads I, II, and III on G. Z., an 18-year-old white man with no evidence of heart disease. Tracings immediately after electroshock show conspicuous rise in T waves and shift in electrical axis.

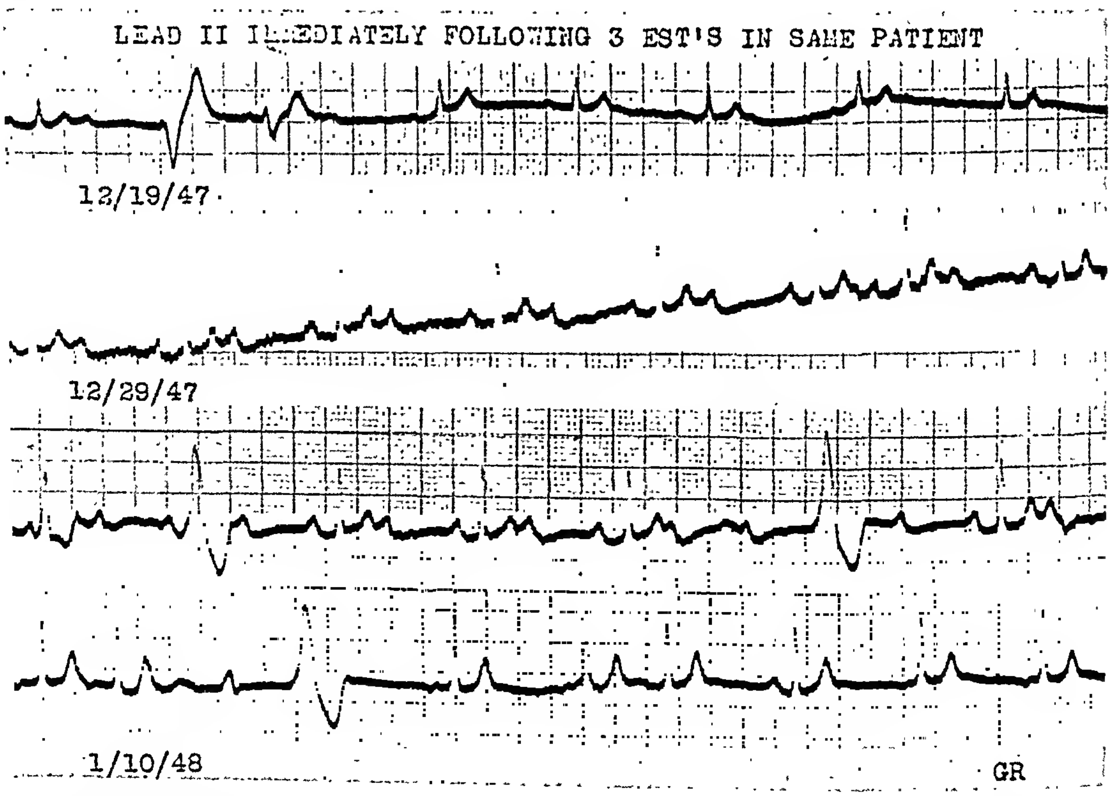

Fig. 7.—Lead II immediately after three different electroshock convulsions on G. R., an 18-year-old white man with no evidence of heart disease. Dec. 12, 1947: Blocked premature atrial impulse followed by two ventricular ectopic beats. Dec. 19, 1947: Periods of 2:1 A-V block. Jan. 10, 1948: Blocked S-A impulses, 2:1 A-V block, and atrial and ventricular ectopic beats. Each convulsion was followed by marked apnea and cyanosis.

Analysis of Serial Tracings.—A comparison was made of successive tracings of each of the twenty-seven patients in whom electrocardiograms had been taken during and after four to seven electroshocks. In seventeen of these patients all electroshock treatments produced essentially the same electrocardiographic changes. In five other patients there were minor variations in form and rhythm following different electroshock treatments, and in the five remaining patients there was definite alteration of response. Fig. 7 shows the arrhythmias immediately after three grand mal seizures in a 20-year-old white man which were all apparently due to increase in vagal tone. A series of tracings in one patient showed gradual improvement in the pretreatment curves, each showing more improvement of a temporary nature immediately after the convulsion. In only one case was there electrocardiographic evidence of increasing myocardial damage on successive electroshock treatments. This patient was a 57-year-old white man whose electrocardiograms are shown in Fig. 8. Increasing subendocardial ischemia was held responsible for a progressive depression of the RS-T segments, which was more marked immediately after each convulsion. In a final tracing a week after the last treatment, the RS-T segments had returned to a normal level.

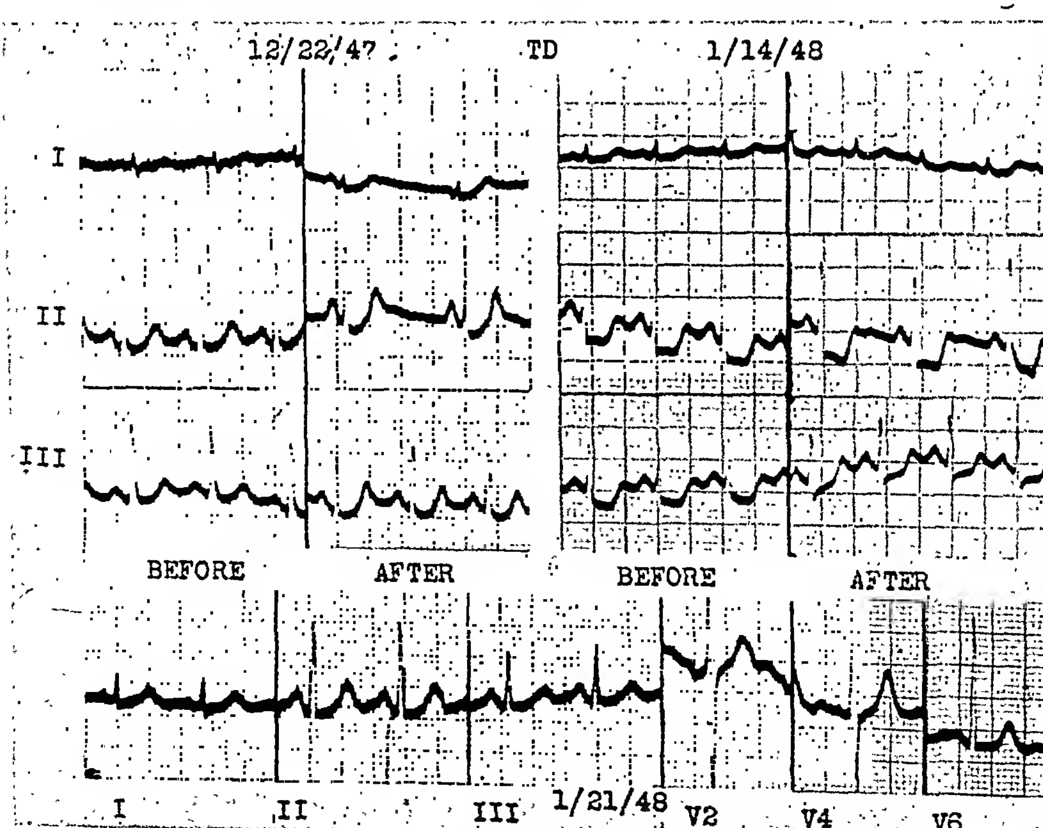

Fig. 8.—Limb leads I, II, and III on a 57-year-old asthenic white man, with original electrocardiogram (Dec. 22, 1947) suggestive of myocardial damage (depression of RS-T_2 and RS-T_3). Note the increasing depressions of RS-T in Leads II and III, and sag of RS-T in Lead I, temporarily made worse by the convulsive episodes of Jan. 14, 1948. Electrocardiograms taken one week following the last electroshock convulsion, Jan. 21, 1948, shows RS-T segments to have regained their normal level.

The Q-T Interval.—A comparison of the Q-T intervals of same cycle lengths in fifty electrocardiograms before and after convulsions revealed a decrease in forty-four instances, no change in five, and an increase in one. The average shortening of the Q-T interval in each case was .038 second. This may well have been a persistence of the effect of the preceding more rapid rate. The QRS complex was often observed to change in height with respiration, particularly in Lead III.

Pretreatment or Prophylactic Treatment.—Preliminary investigations of the value of quinidine and atropine as pretreatment medication were then carried out in selected patients showing potentially serious post-treatment reactions. The results in these cases are considered separately from the original series.

In two patients in whom the base-line electrocardiogram showed evidences of myocardial damage, frequent premature ventricular contractions were noted, beginning after one to two minutes of cyanosis which followed the convulsive seizure. These extrasystoles were abolished in one case and markedly diminished in another by quinidine given orally in dosages of 0.2 Gm. four times daily. In another patient with no evidence of heart disease, many premature contractions of ventricular origin were observed immediately after treatment and then were prevented in subsequent treatments with similar quinidine therapy. It was also noted that early administration of 100 per cent oxygen tended to erase ventricular premature contractions.

In the treatment of the arrhythmias of apparent vagal origin, atropine sulfate was given intramuscularly before electroshock, first in doses of grain 1/150 and grain 1/100 with disappointing effects. Later nine patients with posttreatment arrhythmias attributed to vagal effects were treated with atropine, grain 1/50, intramuscularly, thirty minutes before the stimulus. In six of these patients in whom the reaction did not appear severe clinically, this dosage of atropine abolished the electrocardiographic changes in four and greatly decreased them in two. Two patients showed alarming post-treatment reactions, with nodal rhythm of thirty and forty-five beats per minute, respectively, and little improvement was noted after Prostigmine. In these two patients atropine, grain 1/50, before subsequent treatments markedly lessened the duration and degree of cyanosis and apnea, and the electrocardiographic changes were much less severe. One of these patients was then given grain 1/30 atropine before treatment, and this completely abolished the arrhythmia previously present. In the final patient, cardiac slowing due to nodal rhythm was accompanied in several treatments by retching and vomiting during and after the convulsive seizure. Atropine sulfate, grain 1/50, given on several occasions abolished the gastric symptoms in each instance, and the vagal effects disappeared from the electrocardiogram.

The rate immediately before the stimulus after premedication with atropine was 120 to 130 beats per minute, the mouth was dry, and the pupils were slightly dilated. In most cases where grain 1/50 was used intramuscularly, the rate remained constant during and after the convulsion, respiration was quickly resumed, and no arrhythmias were noted.

Recent Myocardial Infarction.—Two patients with recent myocardial infarction were also given electroshock therapy. One was a 39-year-old white man who

had sustained a posterior infarct six weeks previously. Residual changes consisted of a deep Q_3, negative T_3, and flat T in Lead V_8. Immediately following a grand mal seizure, the record changed, in that T_3 transiently rose to become low-positive. The electrocardiogram of a 52-year-old white woman showed a small Q_2 and sharply negative T_2 and T_3 as residua of a posterior infarct several months previously. There was apparent improvement after the convulsion, with T_2 becoming positive and T_3 flat. In both instances the duration of the changes was only three to five minutes.

DISCUSSION

An increase of electrocardiographic abnormalities has been observed during intense emotional stress and during psychiátric disorders, and has been attributed to autonomic nervous system imbalance. Mainzer and Krause[15] reported pathologically changed tracings during fear of impending operation in twenty-nine of fifty-three patients. Logue, Hanson, and Knight[16] showed variations from normal in 49 per cent of 150 patients with neurocirculatory asthenia, but felt that there was no characteristic electrocardiogram in this condition. Wendkos[17] demonstrated that T waves in precordial leads in emotionally unstable persons may vary from the normal on the basis of increased sympathetic or parasympathetic tone. Heyer, Winans, and Plessinger[18] found electrocardiographic abnormalities in psychotic patients increased to an incidence of 21.5 per cent, as compared to 3 per cent in controls.

In this series, we are reasonably certain of each diagnosis of organic heart disease, since clinical findings were correlated with the electrocardiographic studies in each patient. In three patients not considered to have heart disease, there were noted increases in the P-R interval in the pretreatment tracing with no other abnormality. In each of these three patients the clinical reaction showed prolonged apnea and cyanosis and was associated with marked vagal effects on the heart. In addition, the base-line tracing of one of the fatalities showed a P-R interval of 0.22 second at a rate of 94, and the cause of death on a clinical basis was considered to be cardiac arrest. It is thus suggested that prolongation of the P-R interval may indicate vagotonia and predispose to untoward post-treatment reactions.

Silfverskiöld and Amark[19] in 1943 reported the venous pressure to rise to high values during the tonic phase of the convulsion and to decline gradually during the clonic phase. Arterial pressures likewise increased greatly during the convulsion. Altschule, Sulzbach, and Tillotson[20] found apnea to last from the time of the stimulus to a variable period after the convulsion. They stated that during this time the patients performed the Valsalva maneuver of maximal forced exspiration. The average arterial blood oxygen was found to decrease from 18.83 volumes per cent before the convulsion to 12.86 volumes per cent immediately after, the average pH of arterial blood decreasing from 7.445 to 7.142.

Even in the patients with no evidence of heart disease, the incidence of arrhythmias following the convulsions in this series is considerably higher than that reported in previous studies. One reason for the difference may be that more

abnormalities were recorded because longer tracings were taken. Another possible cause for a variance in results is that all of the patients of this series had preliminary curarization, whereas most of the patients in previous reports were not given curare. Several authors have suspected curare as being a contributing or predisposing factor to untoward reactions. These results would tend to support their view. In the cases in which Prostigmine was given, we noted some improvement in respiration but little in the electrocardiogram.

Our patients with organic heart disease showed an increased susceptibility to premature contractions of atrial and ventricular origin, wandering of the pacemaker, nodal rhythm, blocked sinus impulses, and prolonged P-R intervals. Several of the rhythm disorders were potentially dangerous, such as sinus standstill of two to three seconds on several occasions and runs of rapid premature ventricular contractions. A fatal outcome could be the result of cardiac arrest in such cases, or of ventricular fibrillation superimposed on this condition or developing as a complication of paroxysmal ventricular tachycardia. Since myocardial damage appears to predispose to arrhythmias, there is a greater risk of treatment in such patients.

Theoretical Considerations.—Previous investigators[9, 12] ascribe the postconvulsive arrhythmias to a hyperactivity of the vagus; this is borne out by the disappearance of most of them following adequate atropinization. The reflexes bringing about increased vagus tone probably have their origin in the changes in the respiratory and cardiovascular systems immediately following the convulsion. A lowered blood pH following the convulsion accentuates the vagal effects, as acidosis potentiates the inhibitory effects of acetylcholine.[21]

The increase in cardiac rate during the tonic phase of the convulsion appears to be due to the increased sympathetic tone which is a response to the muscular activity. Direct stimulation of the sympathetic centers may well contribute. The changes in rhythm during petit mal responses are most likely the result of direct central autonomic stimulation, and this, in addition, is a factor in some of the postconvulsive arrhythmias. The evidence for such an origin of cardiac arrhythmias recently has been excellently summarized in an editorial and experimentally demonstrated by Weinberg.[22] It has been shown that stimulation of cardiac sympathetic nerves in lightly anesthetized cats can cause ventricular extrasystoles and ventricular tachycardia.[23] Disturbances of rhythm have been noted following air encephalograms.[24]

An increased irritability of the myocardium due to anoxia and to increased cardiac work is another potential cause of arrhythmias. The increased incidence of abnormalities of rhythm in patients with myocardial damage supports the idea of a local origin caused by myocardial irritability.

A transitory rise in the height of the P waves and depression of the RS-T segments were most frequently noted in Leads II and III, but also occurred in Lead I. They can be explained by the marked increase in the venous return after the sudden cessation of the forced expiratory maneuver, which pools the venous blood in the periphery. A resulting dilatation of the right atrium and overloading of the right ventricle would account for such electrocardiographic changes.

Many of our electrocardiograms showed a temporary elevation of T waves in all leads. In eleven patients with electrocardiographic abnormalities, the immediate post-treatment tracings appeared considerably improved because of this change. Two of our patients with residua of posterior myocardial infarctions showed temporary reversal of negative T waves. Anoxemia and increased muscular exertion would be expected to produce lowering or negativity of the T waves in patients with coronary insufficiency and depression of the RS-T segments. Similar adverse changes may occur in normal persons under stress; they were also described in a study of the electrocardiogram in insulin shock.[25] Electrolyte changes seem the most likely explanation of the occasionally striking T-wave elevations. Acidosis produces significantly taller T waves,[26] and a lowering of the blood pH is known to occur immediately after the convulsion. A release of potassium from the interior of injured muscle cells may be responsible. However, potassium does not make erect the inverted T waves of myocardial infarction, but tends to invert it further.[27]

Conclusions as to Value of Pretreatment Medication.—Only preliminary studies have been done in pretreatment medication in order to avoid complications of therapy. Quinidine therapy in selected cases has been previously recommended by Hayman.[28] Quinidine would seem to be indicated for prophylaxis in patients showing premature ventricular contractions in the pretreatment electrocardiogram. Quinidine sulfate in small doses, orally, has proved effective in three of our cases in reducing or eliminating frequent premature ventricular contractions after the convulsion. Prompt administration of oxygen is also a most worthwhile procedure in such cases.

Atropine has been very effective in eliminating alarming cardiovascular and respiratory reactions in a small group of cases. Bellet and associates[9] noted the disappearance of postshock arrhythmias in three cases in which atropine was given to evaluate the role of increased vagal tone. Larragoiti[29] advised its use in vagotonic patients with a history of "vagal crises" and in prolonged apnea. He also administered atropine in combination with Aminophyllin to patients with coronary disease. We have learned that to obtain the desired effect, atropine must be given in adequate doses, from 1.3 mg. (grain 1/50) to 2.1 mg. (grain 1/30) intramuscularly about thirty minutes before the stimulus. It acts as an effective respiratory stimulant, and long periods of postconvulsive apnea were eliminated in our cases. The usual marked vagal arrhythmias accompanying the alarming reactions were markedly reduced or eliminated by such doses, but smaller amounts were not effective. Prophylactic use of atropine seems to be of value to avoid cardiac arrest, a probable mechanism of some of the fatal reactions. Atropine has recently been found by Wilburne and associates[30] to be of value in experimental animals in preventing ventricular tachycardia, a dangerous mechanism because it may change into ventricular fibrillation and lead to death. Severe retching and vomiting during and after the treatment has been prevented by its use. The mucous membranes are made dry by its action and there is less frothing and less aspiration of mucus. Thus, there would be less chance of developing pulmonary complications.

In view of the rarity of fatal reactions, premedication with atropine is not advised routinely. However, it seems indicated to avoid complications in selected cases, and further studies are being continued in its use. Preliminary atropinization should be seriously considered whenever pretreatment electrocardiograms show prolongation of the P-R intervals, which may be the result of a "vagotonic" constitution. Arrhythmias attributed to vagal effects, prolonged apnea and cyanosis, and postconvulsive vomiting should lead to a consideration of premedication with atropine. It reduced the severity of the convulsive effects in two of our patients to a degree that treatments did not have to be abandoned, and the patients were thus enabled to get the psychiatric benefits of electroshock therapy.

GENERAL SUMMARY

An analysis is made of electrocardiographic changes following 304 electrically induced major convulsions and twenty-three minor convulsions in 126 curarized patients. Tabulation of the disturbances of rhythm shows them to be more frequent than was previously supposed; there is an increased incidence in patients with organic heart disease.

Although no deaths were observed, some of the arrhythmias were potentially dangerous. A postconvulsive increase in vagus tone appears to be the principal mechanism, although the local irritability of the myocardium is an additional factor.

Higher P waves and depressions of RS-T segments frequently occurred; they were apparently due to transient dilatation of the right atrium and overloading of the right ventricle after the convulsion.

A prominent elevation of T waves, probably the result of electrolytic changes, occasionally occurred and produced apparent brief improvement in the electrocardiogram.

Quinidine, given orally, and the early administration of oxygen after the convulsion have proved of value in preventing frequent premature ventricular contractions.

Adequate atropinization in selected cases shows much promise in reducing the severity of the postconvulsive apnea and cyanosis and in preventing cardiac arrhythmias. Postconvulsive vomiting has been relieved by atropine premedication, which dries the mucous membranes and reduces aspiration.

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ON THE MEASUREMENT OF THE QRS COMPLEX AND THE INTERPRETATION THEREOF BY DIRECT AND INDIRECT DEDUCTION

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In analyzing the QRS complex, the usual procedure is to measure the duration of the different components of this complex along the isoelectric line. We are of the opinion that another method of measuring is more satisfactory.

F. N. Wilson, in dividing the semidirect lead into two parts, has said, "The records actually obtained represent the algebraic sum of (1) an R wave of the kind described, written by the muscle between the exploring electrode and the ventricular cavity, and (2) a downward deflection, representing the potential variations that would occur at the epicardial surface as the result of excitation of the other parts of the ventricular wall alone."

Considering that no sharp distinction can be drawn between (1) and (2), it is difficult to use this representation as a basis for a quantitative analysis of the QRS complex.

One might, however, view the semidirect lead as the algebraic sum of the differences of potential between the exploring electrode and a point within the ventricular cavity nearest the electrode, on the one hand, and between this latter point and the indifferent electrode, on the other. The blood being a better conductor than the tissues of and outside the heart, it frequently makes very little difference where this point is located in the ventricular cavity. To avoid minor difficulties it is best, however, to select for this point a site in the ventricular cavity nearest to the exploring electrode.

The potential of the endocardial point under consideration in respect to the indifferent electrode, hereinafter termed endocardial potential, either will be negative during all of systole, or, if the septum is first heterolaterally activated, it will be positive at the start of systole and negative later.

The difference of potential between the exploring electrode and the endocardial point, hereinafter termed subepicardial difference of potential, can, however, only be positive and will be so only as long as the activating dipole layer is between these two points, with its positive side directed toward the exploring electrode. Before and after this period the potential difference will be zero.

The algebraic sum of the two differences of potential gives us the semidirect electrocardiogram. This is shown in Fig. 1.

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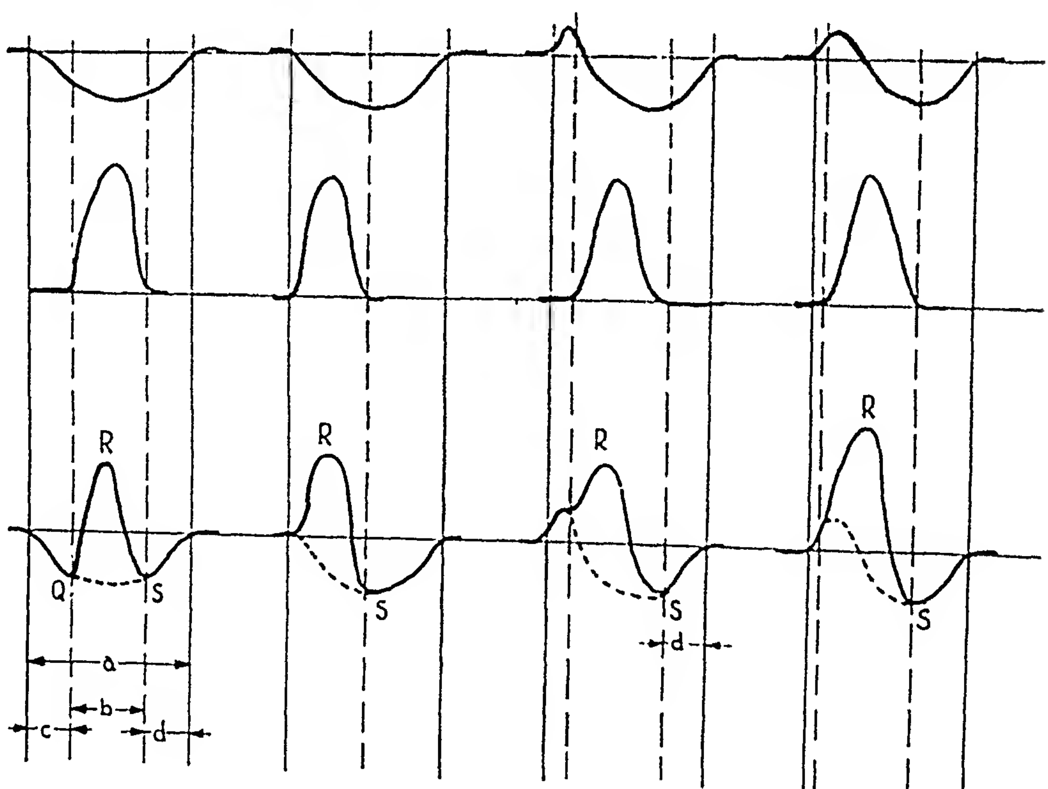
In general, the subepicardial potential difference presents a much steeper slope, as a function of time, than does the endocardial potential when it is negative, because the latter is subject to influences from all parts of the ventricular muscle more or less dispersed in time (see Appendix II).

This is what enables the observer to distinguish clearly in most electrocardiograms just when the subepicardial potential difference starts to assume a positive value and when it returns to zero, that is, the length of time which the electric dipolar layer accompanying the activation requires to move from the endocardial to the epicardial point. It is reasonable, therefore, when a Q is present (see Fig. 1) to measure the width of R not along the isoelectric line, but between its lowest points, that is, between the lowest point of Q and the lowest point of S, if this wave is present. The important intervals of time to measure are the total width of the QRS complex (*a* of Fig. 1), the duration of the R wave, measured at its lowest points (*b* of Fig. 1), the interval between the beginning of the QRS complex and the lowest point of the Q wave (*c* of Fig. 1), and the interval between the lowest point of the S wave and the end of the QRS complex (*d* of Fig. 1).



Figs. 1-4.—The four graphs in the top row represent the endocardial potential as a function of time; the middle row, the subepicardial potential difference; and the bottom row, the QRS complex of a semidirect electrocardiogram. The lowest four complexes are the algebraic sum of the complexes in the two preceding rows.

If, however, a Q wave is absent, two possibilities exist. Either the wall of muscle between the exploring electrode and the endocardial point is activated from the very beginning (Fig. 2), or the septum is first activated heterolaterally (Figs. 3 and 4). In actual practice these two possibilities are often difficult to distinguish (compare Fig. 2 and Fig. 4). If, however, the ascending limb of the R wave shows a notch anywhere (Fig. 3), this will sometimes clearly indicate the moment when the activation of the interjacent muscle wall begins,* as is seen frequently in cases of right bundle branch block.

Beside the logical connection which it has with the production of the various parts of the electrocardiogram, our method of measuring possibly has the further advantage of its results being quantitatively less dependent on the apparatus employed, for the moment at which the deflection begins to move in another direction is surely less affected by the inertia of the apparatus than the moment at which the zero line is crossed.

In a normal semidirect electrocardiogram of the QRS complex, the interval indicated by *a* of Fig. 1 measures the time needed to activate the whole of the ventricular muscle; that indicated by *b* of Fig. 1, the time needed for the activating dipole layer to move from the endocardial surface outward through the muscular wall to a point just beneath the exploring electrode; and that indicated by *c* of Fig. 1 measures the time between the beginning of activation of the ventricular muscle and the beginning of activation of that portion of the muscle wall between the exploring electrode and the endocardial point which has been referred to. The duration of the interval shown in *d* of Fig. 1 indicates the time that elapses between the completion of the activation of the subepicardial point beneath the exploring electrode and the completion of the activation of the entire ventricular muscle.

We shall now investigate what determines the duration of the endocardial curve and the subepicardial curve.

Duration of Endocardial Curve.—Many factors combine to determine the duration of the endocardial curve: the rate of conduction through the Purkinje tissues, the length of the latter, the thickness of the cardiac muscle, and the rate at which the dipole layer is propagated through the ventricular muscle.

The rate of propagation through the Purkinje tissues is roughly 4.0 meters per second and the maximum length of these tissues (the inflow tract of the left ventricle, or the distance from the mitral valve to the apex) is about 70 millimeters. Hence, if the inflow tract is lengthened by 100 per cent, the time needed to pass along is increased by 17.5 milliseconds. The rate of propagation of the dipole layer is much lower, about 0.4 meter per second. If the thickness of the cardiac muscle is 7 millimeters and it becomes twice that, then the time needed for the dipole layer to pass through will be increased by 17.5 milliseconds. Both increases in time are important and lengthen the endocardial curve appreciably.

It is to be expected that under abnormal conditions, such as ischemia or fibrosis, a change will take place in the rate at which the dipole layer is propagated through the cardiac muscle. Unfortunately, our knowledge regarding these changes of rate is still insufficient.

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*Not every notch on the ascending limb of the R wave is the result of such activation.

Duration of Subepicardial Curve.—The duration of the subepicardial curve is determined by two factors: the thickness of the cardiac muscle and the rate at which the dipole layer is propagated through this muscle.

If in the semidirect electrocardiogram we find a lengthening of the subepicardial curve of about 10 milliseconds and if the same is observed in various parts of the ventricle, there is very probably a thickening of the cardiac muscle. If the activation of this group of muscles is the last to be completed, then the endocardial curve will also be longer, for a local thickening of the cardiac muscle practically never occurs.

A local lengthening or shortening of the subepicardial curve indicates, therefore, a local change in the rate of propagation in the cardiac muscle.

If in a semidirect electrocardiogram there occurs a lengthening of the endocardial curve by about 10 milliseconds without there being a lengthening of the subepicardial curve, then we are dealing with dilatation of the heart or with slowed conduction in the Purkinje tissues. When conduction in these tissues is deranged, other changes often occur in the electrocardiogram and these sometimes facilitate further analysis. Furthermore, a pronounced dilatation of the ventricle can naturally be determined by x-ray examination.

There are many possible combinations, but we shall not enter into this subject in detail here. We may perhaps merely point out that the duration of the interval indicated in *d* of Fig. 1 determines the moment at which the subepicardial point is activated; when this interval is large this point is activated early; when it is small the activation is late.

SUMMARY

A new method of measuring the QRS complex is suggested. This method supplies data with regard to the condition of the cardiac muscle which so far it has been impossible to obtain.

APPENDIX I

The length of the interval *a* of Fig. 1 is dependent on many factors. Hence, the first thing we determine is the length of the interval *b* of Fig. 1. For this purpose we usually use Lead V_5.

Electrocardiograms were made of 102 patients in all, and the results were as follows: In eighty-one cases the length *b* was less than 64 milliseconds, in twenty-one it was longer than 64 milliseconds, and varied between 64 and 100 milliseconds. On clinical grounds it may very probably be assumed that seventeen of the latter group of patients were suffering from hypertrophy of the left ventricular muscle. In two cases hypertrophy was a possibility; in the remaining two, hypertrophy of the left ventricular muscle was unlikely.

APPENDIX II

The Origin of Endocardial Potential and of Subepicardial Potential Difference.—Let us imagine the ideal case of a heart consisting of one chamber only, enclosed on all sides by a wall, the openings in which are so small as to be negligible, and,

furthermore, let us imagine that at a given moment this wall, over its entire inner surface, is completely occupied by a dipole layer with a constant dipole density per square centimeter of μ. Let us suppose also that this dipole layer, without change of dipole density, works its way outward through the wall and reaches simultaneously its entire outer surface and then suddenly disappears.

Under the influence of this dipole layer, no difference of potential would then arise between the epicardial point and the indifferent electrode. As long as the dipole layer was in existence, the endocardial potential would be just $-4\pi\mu$ in electrostatic centimeter-gram-second units, but in a direct lead this would be exactly neutralized by the subepicardial potential difference, which would then be $+4\pi\mu$. This would be the case because the direct lead is equal to the difference between the endocardial potential and the epicardial potential.

A real heart, however, consists of two chambers with large openings and all parts of the surface of its walls are not activated at the same time. Hence, if only a small portion of the wall is occupied by a dipole layer, the endocardial potential will be only slightly negative, even immediately beneath the particular bit of the activated wall. The endocardial potential will not be greatly influenced by the position of the endocardial point; the subepicardial potential difference is, however, very greatly dependent on the position of the epicardial point with respect to the dipole layer.

As a result of the various parts of the wall being activated successively, the endocardial potential will show a relatively flat curve and will remain less than $-4\pi\mu$, unless one ventricle, or both ventricles taken as a whole, should happen to be surrounded on all sides by the uninterrupted dipole layer. In this connection an average value for μ should be taken.

Quite different is the behavior of the subepicardial potential difference. As long as there is no dipole layer between the endocardial and epicardial points, the potential difference between the two will vary little from zero. As soon, however, as a dipole layer comes into being between these points or a neighboring dipole layer extends so as to lie between them, a potential difference between these points will arise comparatively suddenly, the difference amounting to from 2π to $4\pi \times$ dipole density per square centimeter in that spot.

Clinical Reports

MORGAGNI-ADAMS-STOKES ATTACKS CAUSED BY TRANSIENT RECURRENT VENTRICULAR FIBRILLATION IN A PATIENT WITHOUT APPARENT ORGANIC HEART DISEASE

A Case Report

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VENTRICULAR fibrillation was assumed to be a very probable cause of sudden death in man by MacWilliam[27] as early as 1889, long before the introduction of the electrocardiograph in clinical practice. He reached this conclusion after studying experimentally induced ventricular fibrillation in animals. In 1850, Hoffa and Ludwig[15] had been able to demonstrate that faradization of the heart of animals led to ventricular fibrillation and death. In 1912, Robinson[36] recorded electrocardiographically short periods of ventricular fibrillation in two patients after clinical death. The duration of the disturbances in the two patients was four and one-half and twenty minutes, respectively. Three years later, Halsey[11] reported a longer attack of terminal ventricular fibrillation. Since then, many cases of terminal ventricular fibrillation have been described.[13,18,28,48] The correctness of MacWilliam's assertion has, therefore, been proved.

Transient attacks of "well established ventricular fibrillation" were recorded for the first time by Robinson and Bredeck[37] in 1917. The patient had repeated Adams-Stokes attacks and pronounced cardiac insufficiency, and died thirty hours later during another episode of fibrillation. Since this observation a number of other cases of transient ventricular fibrillation have been reported.[7,9,10,17,20,26,29,32,33,39,40-47,56,57]

It appears from the reports that the cause of both the terminal and the transient form of ventricular fibrillation is always to be found in association with organic disease of the heart, most often coronary sclerosis or thrombosis with infarction. Frequently there is also present complete A-V heart block.[5,7,9,10,20,32,33,39,40,47,56]

From Krohgstøtten Hospital, Oslo, Norway.
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It has not been possible to find any report of an electrocardiographically verified case of purely functional transient ventricular fibrillation of somewhat long duration. As early as 1911, Hoffmann[17] mentioned a case of transient ventricular fibrillation which was recorded at the close of an attack of tachycardia in an apparently healthy young woman. Halsey doubted whether the brief attack of diphasic oscillations (three seconds) was really an example of ventricular fibrillation. Rasmussen[34] published an electrocardiogram which resembles one of the electrocardiograms (Fig. 4) obtained from our patient immediately before the attack of ventricular fibrillation. It presented a succession of ventricular extrasystoles, which is the pathognomonic precursor of ventricular fibrillation. Rasmussen's patient did not faint during this attack, which lasted only two and one-half seconds, but later he had several Adams-Stokes attacks. It is probable that during these syncopal attacks well-developed ventricular fibrillation was present, but the attacks were not recorded. As in Hoffmann's case, no organic heart disease was discovered in Rasmussen's patient. A case described by Bjerlöv[1] in 1932 as an example of ventricular fibrillation with recovery has since been considered by Öhnell[59] to have been an example of the Wolff-Parkinson-White syndrome with paroxysmal tachycardia. Between the attacks of tachycardia the electrocardiogram always showed bundle branch block and a short P-Q interval. Öhnell has reported a case of Wolff-Parkinson-White syndrome with a similar electrocardiogram.[58]

The case which is to be reported is believed to be the only case of ventricular fibrillation of functional origin that has been recorded electrocardiographically (Fig. 1).

CASE REPORT

An engineer, 38 years of age, was admitted to the Krohgstøtten Hospital because of attacks of syncope. The past history was not significant; he had not had rheumatic fever or chorea. He had had no cardiovascular symptoms until the spring of 1943 when he began to notice attacks of palpitation. Even after this symptom developed, he had no shortness of breath, chest pain, or edema. The attacks of palpitation seemed to be made worse by smoking. They were not related to exertion; indeed, he was more conscious of the disturbance when he was at rest. After the attacks of palpitation had been present for one month, he consulted a physician, who discovered nothing on clinical or radiological examination of the heart; electrocardiograms were not taken at this time.

The attacks of palpitation were always quite transient until January, 1944, when they became more frequent and more prolonged. On the evening of Jan. 24, 1944, the patient fainted while sitting at his desk in his home. Observers estimated that he was unconscious for approximately two minutes. On the next evening he fainted while working at his desk at his place of work. After four attacks of syncope during the morning of Jan. 26, 1944, he was admitted to the hospital.

On admission he was perspiring, his skin was cold, and he looked ill. However, he stated that he had felt well before and after the attacks. While being initially examined, he had three or four syncopal seizures. Between attacks the pulse rate was 70 to 90 per minute. The rhythm was quite irregular because of isolated extrasystoles or short runs of extrasystoles. In the bebinning of an attack it was observed that the pulse and heart sounds became imperceptible for eight to ten seconds; fainting then occurred, but the only suggestion of a convulsion was the presence of slight twitching of the leg muscles immediately after one attack. There was no vomiting or incontinence during the attacks. At the initial examination, electrocardiograms were taken immediately before, during, and after an attack.

The first group of four simultaneous tracings (Fig. 1) shows at its beginning a normal sinus rhythm with a rate of 70 per minute. There then appears a run of approximately ten deformed ventricular complexes which is initiated by an extrasystole This episode lasted for 2.6 seconds. Although the pulse could not be felt and the patient felt "a little queer," he did not lose consciousness. The next group of four simultaneous tracings shows extrasystoles, at first singly, and later in short runs. The continuous electrocardiogram at this point was stopped. A few seconds later, the patient became unconscious and the electrocardiogram in the third group of tracings was recorded (Lead I and Lead II). During this period of ventricular fibrillation, the ventricular complexes are sometimes fairly regular but the shape of the waves differs considerably. No P waves can be seen. This episode of ventricular fibrillation lasted 17.7 seconds. The ventricular rate was 360 per minute at the beginning and 390 per minute at the end of the attack. At the end of the attack of fibrillation, a slow sinus rhythm is present. After two cycles of this mechanism, the P waves disappear, possibly as a result of the onset of nodal rhythm.

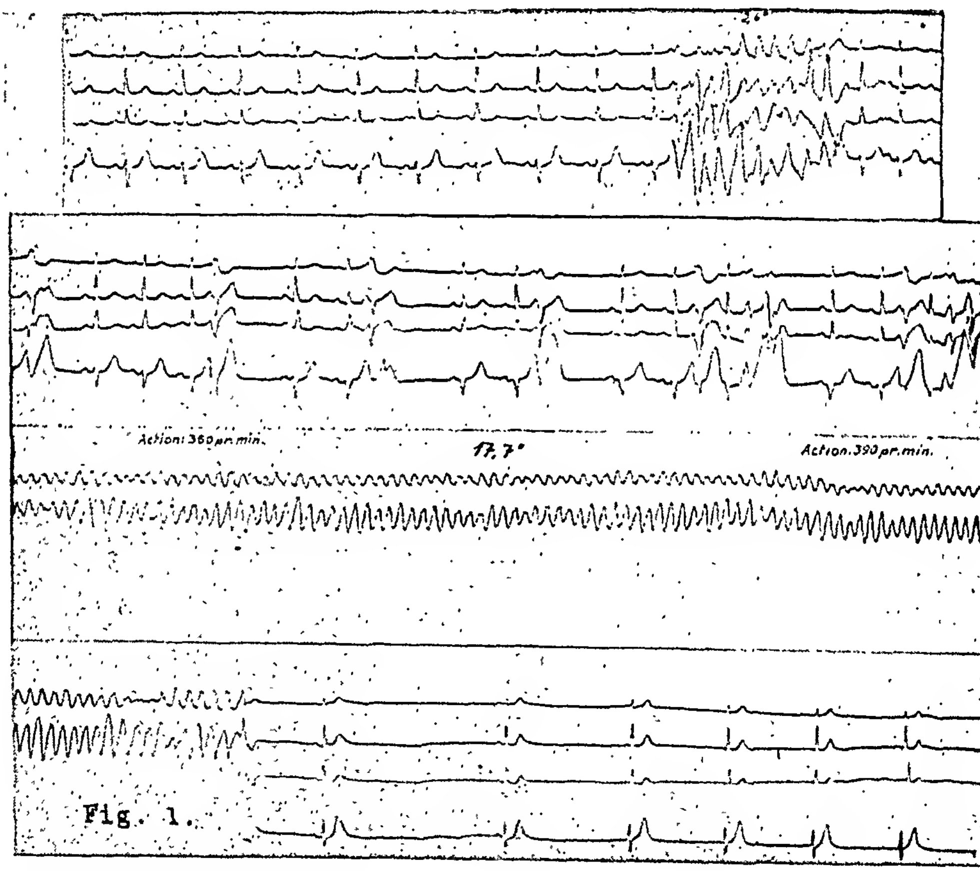

Fig. 1.—After a period of sinus rhythm followed by a number of deformed ventricular complexes, electrocardiogram shows ventricular fibrillation and then sinus bradycardia and A-V nodal rhythm. The different parts of the electrocardiograms are continuous except for some seconds just before the patient developed the Adams-Stokes attack. When he fainted the electrocardiogram was immediately resumed.

During the period of ventricular fibrillation, no pulse was perceptible and respiration ceased. The tracing which was made during this attack and which has just been described was not available to us for two hours. Before we saw the recorded tracing, the patient was given 1.0 ml., and after one-half hour, an additional 0.75 ml. of adrenaline, subcutaneously, as the attacks recurred. When the electrocardiogram was available and the mechanism observed, the patient

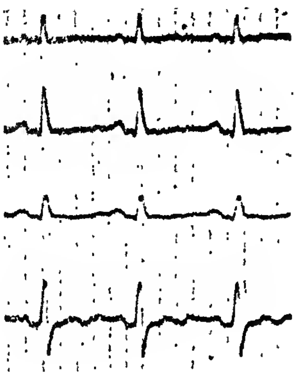

Fig 2.

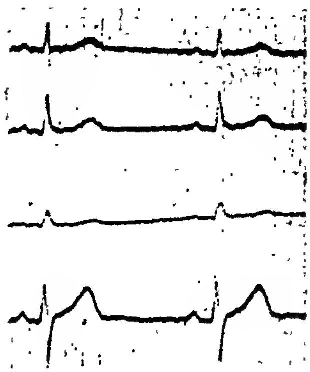

Fig. 3.

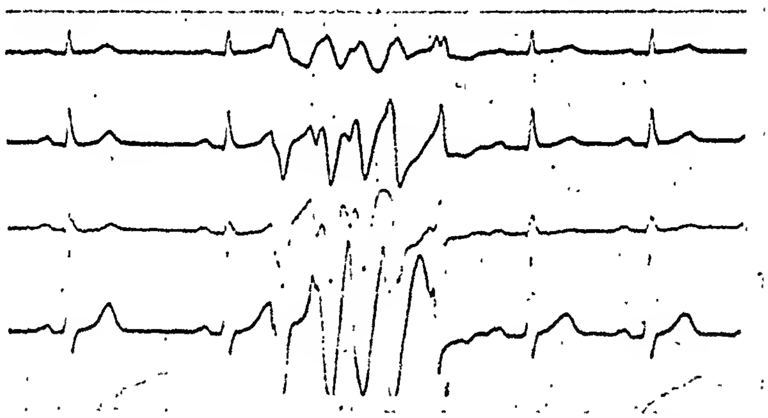

Fig. 4.

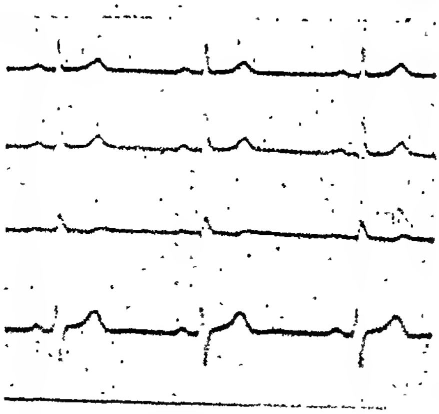

Fig 5

Fig. 2.—The electrocardiogram taken the day after the attack illustrated in Fig. 1 shows flattened T waves in the standard leads.

Fig. 3.—A normal electrocardiogram taken two days after the attack illustrated in Fig. 1.

Fig. 4.—At a control examination one week after the attack the electrocardiogram shows a brief run of extrasystoles.

Fig. 5.—Electrocardiogram taken three years after the attack is quite normal.

was given 0.20 Gm. of quinidine sulfate by mouth. At the end of four hours, he had received, in all, 0.60 Gm. of quinidine sulfate. At this time the syncopal attacks ceased, though the patient noticed occasional extrasystoles. Within seven hours after the electrocardiogram was taken, he had received, altogether, 1.0 Gm. of quinidine sulfate.

On the day of admission, before the heart was brought under the influence of quinidine, the patient had, in all, ten attacks of syncope. The shortest attack lasted 17.7 seconds (the attack shown in Fig. 1) and the longest attack lasted for some seconds over two and one-half minutes. On the day after his admission he received, in all, 1.0 Gm. of quinidine by mouth. Thereafter, he continued to receive 0.20 Gm. of quinidine orally per day.

It will be noticed that the T waves shown in Fig. 1 are normally upright. A tracing taken two days after admission (Fig. 2) shows the T waves to be flattened in the indirect leads. A tracing taken two days later (Fig. 3) is quite normal.

During his hospital stay, studies other than electrocardiographic observations were normal. The blood pressure on several occasions was 120/80. Radiographic studies of the heart showed no abnormality. The hemoglobin, red and white blood cell counts, and the differential count were normal. The erythrocyte sedimentation rate was 4.0 mm. in one hour. The serum cholesterol was 110 mg. per cent. On the evening of admission the patient had a slight temperature, but thereafter he was afebrile. He remained in the hospital for a fortnight and was discharged in good health. He was directed to take 0.20 Gm. of quinidine three times a day.

One week after he had been dismissed from the hospital he was re-examined. He had been entirely free of symptoms except for consciousness of occasional extrasystoles. However, a tracing taken at this time (Fig. 4) did record a run of five extrasystoles. At the patient's express request, he was allowed to discontinue quinidine. Three months after discontinuing the drug, he was again admitted to the hospital because of recurrence of syncopal attacks. During this second hospital admission, we did not succeed in recording any attacks of ventricular fibrillation electrocardiographically. The patient was then discharged on 0.10 Gm. of quinidine sulfate, orally, twice a day; this was subsequently reduced to 0.10 Gm. once a day. The patient has been re-examined twice and has continued to be entirely free of symptoms except for a very occasional extrasystole. The small dose of quinidine has been continued. An electrocardiogram (Fig. 5) made Jan. 5, 1947, almost three years after his original admission, is entirely normal.

DISCUSSION

Two other disturbances of rhythm are so frequently associated with the development of ventricular fibrillation that it is difficult to avoid the conclusion that these disturbances have a causative relationship to ventricular fibrillation. One is ventricular extrasystolic disturbances and the other is complete A-V heart block.

Increased impulse formation due to ventricular extrasystoles has been frequently observed to precede the onset of ventricular fibrillation. Schwartz[39] has stated that if in a patient with complete A-V heart block there is observed an increase in the basal ventricular rate (for example, from 38 to 65 per minute) due to an extrasystolic disturbance, subsequent syncope in such a patient can be assumed to be the result of the occurrence of ventricular fibrillation.

The importance of complete A-V heart block in the development of ventricular fibrillation has been particularly emphasized by American authors.[7,9,10,20,32,33,39,40,47,56] Davis and Sprague[5] hold that A-V heart block is the pathogenetic basis for the occurrence of ventricular fibrillation and that it is the improvement in A-V conduction that brings the fibrillation to an end. Theoretically, say these authors, one might expect an eventual "circus move-

ment" in the ventricle to be interrupted by the excitation wave from the auriculoventricular node. Rasmussen[34] produced ventricular fibrillation experimentally in exposed hearts of dogs by clamping the pulmonary artery and the aorta. The longer the clamp was applied, the longer became the P-R interval until, finally, complete A-V block developed. The latter was soon followed by either ventricular fibrillation or ventricular standstill.

Ventricular fibrillation is, therefore, not only dependent upon impulses of high frequency from one or more centers, but also upon disturbances of conduction. In brief, several factors seem to be required to bring about ventricular fibrillation. There usually exists serious organic disease of the heart, such as coronary sclerosis or coronary thrombosis with infarction. The anoxia that ensues leads to greatly increased irritability of the ventricles; then, if for the same reason conductional disturbances arise, especially complete A-V block, ventricular fibrillation may easily be evoked as a result of the absence of the normal excitation wave that would have rendered the ventricles refractory.

In an organically sound heart with no disturbance in the conducting system it seems to be very difficult for ventricular fibrillation to develop. Wiggers[54, p. 537] believes that when it does arise, recovery is rare in man and in other large animals. The heart of the smaller animal (rat, cat) is more likely to recover spontaneously.

Ventricular tachycardia of functional origin has been recorded by several investigators,[6,8,21] but well-established functional ventricular fibrillation has not been recorded in man. In our case no organic heart disease existed nor any form of heart block. Thus, it seems that impulses of high frequency are alone sufficient to evoke ventricular fibrillation.

A feature of particular interest is the fact that the attacks continued during the administration of adrenalin and were unaffected, apparently, by this drug. It is likewise remarkable that the patient survived so many seizures, sixteen in all. This again shows that an organically sound heart can withstand numerous attacks of ventricular fibrillation.

Several authors[7,8,51] have pointed out that the T waves become negative after ventricular paroxysmal tachycardia and ventricular fibrillation. In our case there was no change in the T waves immediately after the seizures (Fig. 1). Not until the next day (Fig. 2) did the T waves become flat in the three standard leads and diphasic in Lead IV. Two days later the electrocardiogram (Fig. 3) was completely normal.

When a case of Adams-Stokes disease is being considered, complete A-V heart block with ventricular standstill usually is thought of first as the responsible mechanism. It is now held by several authors[16,32,33,38,57] that Adams-Stokes attacks are equally often, or even oftener, the result of ventricular tachycardia or ventricular fibrillation.

Treatment.—Quinidine sulfate, by mouth, is generally recognized to be an effective remedy in treatment of ventricular paroxysmal tachycardia and paroxysmal ventricular fibrillation. However, cases have been reported in which ventricular fibrillation has been evoked by the use of quinidine. This has occurred especially where there existed a serious myocardial lesion secondary to

coronary thrombosis and where the conduction system was damaged with resulting complete A-V heart block. Quinidine reduces all of the functions of the cardiac muscle. If quinidine has a greater effect in prolonging the conduction time than in prolonging the refractory period, it will be more likely to evoke rather than to prevent or put an end to ventricular fibrillation.

Kerr and Bender[20] believed that quinidine sulfate was the cause of ventricular fibrillation in their case. Davis and Sprague[5] presented a similar case, in which, however, the patient had also been given digitalis which may have been a contributory factor. Schwartz and Jezer[45] gave small doses of quinidine sulfate, intravenously, to two patients with A-V block, who then developed transient attacks of ventricular fibrillation. They believe, therefore, that quinidine, given by mouth, may also evoke ventricular fibrillation in susceptible patients. Jervell[18] reported two cases of cardiac infarction with ventricular paroxysmal tachycardia in which quinidine was given intravenously. One of the patients collapsed, but afterward recovered. The other died immediately after the injection.

White[53] has stated that there have sometimes been seen strikingly good effects from intravenous injection of quinidine sulfate, but that it is simpler, safer, and probably equally effective to administer this drug orally. It has been reported by Brinchmann[4] that large doses of quinidine have been given by mouth for several years without injurious effects. In only exceptional cases does quinidine, given orally, induce ventricular fibrillation.

Levine[23] showed in experiments on cats that quinidine prevented the onset of ventricular fibrillation by increasing the refractory period. He, therefore, finds it rational to use quinidine in ventricular fibrillation. Blumenthal and Oppenheimer[2] showed by experiments that quinidine renders the heart refractory to substances that bring on ventricular fibrillation.

As in experiments on animals, the good effects of quinidine in patients with ventricular tachycardia and ventricular fibrillation is most probably due to the fact that prolongation of the refractory period is the predominant effect of the drug. Even though given in small doses (0.20 Gm., by mouth, five times in seven hours) quinidine in our case is believed to have prevented recurrence of the attacks. After the last attack our patient has been taking 0.10 Gm. of quinidine sulfate by mouth, daily, and has had no attack for three years.

SUMMARY

1. The case of a healthy young man who had numerous Adams-Stokes attacks is presented. An electrocardiogram recorded during an attack which lasted 17.7 seconds showed typical ventricular fibrillation. The longest attack lasted some seconds over two and one-half minutes. Since the patient has shown no evidence of organic heart disease over a period of three years, it is believed that the ventricular fibrillation must have been of purely functional origin.

2. The pathogenesis of ventricular fibrillation is briefly discussed: both hyperirritability of the ventricles (ventricular extrasystoles) and complete A-V

heart block must be present in almost all cases in order that ventricular fibrillation develop. In some instances, as in the presented patient with an apparently sound heart, hyperirritability may be sufficient to produce ventricular fibrillation.

3. The use of quinidine for treatment of ventricular fibrillation is discussed. In the author's case it is probable that quinidine, administered by mouth, prevented recurrence of the attacks.

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TUBERCULOUS FALSE ANEURYSM OF THE ABDOMINAL AORTA WITH RUPTURE INTO THE STOMACH

A Case Report with Review of the Literature

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Tuberculous mycotic aneurysm of the aorta is a rare condition. In 1944 Owens and Bass[1] reported an instance of this condition occurring in the abdominal aorta and reviewed the twenty-one such cases published previously. In all of these twenty-one cases the aortic lesion had resulted from involvement of its wall by an adjacent tuberculous lymph node and this was apparently the mechanism in the case to be presented in this paper. In the case reported by Owens and Bass[1] and in the unpublished case of Brooks and Dawson,[2] the aneurysm, which was thoracic, had resulted from hematogenous tuberculous infection of the aortic wall. The latter named case is noted because of its similarity to the former in spite of its location above the diaphragm. No adjacent tuberculous lymph nodes were found at autopsy in these patients and acid-fast bacilli were demonstrated in the aortic lesion.

The case of Brooks and Dawson[2] was that of a 45-year-old man, admitted for intense continuous epigastric pain and vomiting of small amounts of bright blood. He died two days later, after massive hematemesis. Autopsy showed fibrocaseous tuberculosis of the upper lobes of both lungs, a tuberculous false aneurysm of the descending aorta which had ruptured into the esophagus, acid-fast bacilli in the wall of the aneurysm, and several mediastinal nodes containing small tuberculous lesions, none of which had ruptured into the aorta. This case and that of Owens and Bass are primary mycotic aneurysms, as defined by Crane,[3] that is, "a lesion developing in the wall of an artery, which is not associated with any demonstrable intravascular inflammatory focus, as bacterial endocarditis, or with any in the surrounding tissue." The instance of tuberculous aneurysm to be presented here, like those previously reported, while mycotic, is not primary in this sense since the aortic lesion was an extension from an adjacent tuberculous area.

The stomach is not a common site of rupture of aortic aneurysm. Rottino[4] in 1943 reviewed thirty-one reported cases of abdominal aortic aneurysm which had ruptured into the gastrointestinal tract. Hunt and Weller[5] in 1946 supplemented Rottino's report by including a case of their own and bringing the number

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Table I. Clinical and Pathologic Findings in the Case Being Reported and in Three Cases Which Were Either Omitted From or Occurred Since Last Review

CASE	DATE	AUTHOR	AGE	SEX	PERTINENT HISTORY LEADING TO ADMISSION	CLINICAL OBSERVATIONS	COURSE	PATHOLOGIC FINDINGS
42*	1931	Bogazzi[6]	70	M	Hematemesis and melena	Profound anemia and emaciation; epigastrium tender and resistant	Death four days after admission following continued hemorrhage by bowel	Tuberculous false aneurysm of the aorta; rupture into the duodenum; erosion through tuberculous lymph node; tuberculous infiltration of adventitia and media of aorta, of duodenal wall, of bodies of three lumbar vertebrae, and of lungs with cavitation
43	1947	Balice[7]	31	M	Attacks of intense epigastric pain	Exploratory operation revealing pulsating mass behind stomach; serologic tests for syphilis equivocal; penile sore, 20 years of age	Readmission six weeks after operation; gross hematemesis and death in a few hours	Aneurysm $7.0 \times 3.5 \times 3.0$ cm. arising from aorta between superior and inferior mesenteric arteries; rupture into third portion of duodenum; hyalinization and fibrosis of wall with perivascular round cell infiltration
44	1947	Cleland[8]	65	F	Collapse and profuse hematemesis	Pulsating tumor in epigastrium; psychosis; Wassermann of blood and spinal fluid negative	Six days after first hematemesis, epileptiform seizure followed by gross hematemesis and death	Aneurysm of aorta 3.7 cm. in diameter; aorta 3.0 cm. above bifurcation with adhering duodenojejunal junction; rupture into jejunum; extensive atheroma
45	1948	Scott, Grimes, and Maxwell	49	M	Profuse hematemesis	Subtotal gastrectomy, after equivocal x-ray findings, with recovery; serologic test for syphilis negative; no evidence of ulcer in operation	Readmission six days after discharge on account of abdominal pain; hematemesis repeated with death twelve days after readmission	Localized tuberculous aortitis; false aneurysm 3.0 cm. in diameter arising from aorta just above celiac axis with rupture into stomach 2.0 cm. below esophageal ostium; stomach adherent to aneurysm; scarred lung apices; caseous tracheobronchial lymph node; miliary tuberculosis of liver and spleen

*Numbered in sequence with cases reported by Rottino[4] and Hunt and Weller.[5]

to forty-one. Of these only five had ruptured into the stomach. Bagozzi's[6] case, reported in 1931, was omitted from these two reviews. It was an instance of rupture of a tuberculous false aneurysm into the duodenum. The type of aneurysm resembled closely the one to be presented here. It is tabulated with two others reported since Hunt and Weller's review[5] (Table I). These with the case to be presented here bring the total to forty-five, only six having ruptured into the stomach. Thirty-five had ruptured into the duodenum, three into the jejunum, and one into an unspecified portion of the small intestine.

The frequency of rupture into the duodenum is probably dependent on the anatomic factor of relative immobility of the duodenum compared with the stomach and the small intestine. It is noteworthy that in seven of the cases of rupture into the stomach and small intestine, adhesion of the aneurysm to the viscus involved is described, as in the case to be presented. In the only two exceptions pathologic details are lacking. Quite aside from this evidence, it would appear that a necessary condition of rupture into a hollow viscus is fixation either by structure or by pathologic adhesion.

The following case is, therefore, presented because of two unusual features: its tuberculous nature and its rupture into the stomach.

CASE REPORT

A 49-year-old white railroad machinist was admitted to the Good Samaritan Hospital, Lexington, Ky., on Dec. 5, 1945, following a gastrointestinal hemorrhage. Twenty years before admission he had had pneumonia, complicated by empyema. He had been in good health following this illness until two years before admission, at which time he had an episode of repeated vomiting and was told by his physician, after x-ray examination of his stomach, that he had a duodenal ulcer. He was placed on a bland diet which he soon abandoned. As he had no food intolerance and no further vomiting, he returned to his work. Three weeks later he vomited a large amount of blood and passed tarry stools. He was, therefore, referred to the hospital on the following day.

Physical examination revealed a well-nourished man in mild shock. His temperature was 98.6°F., pulse rate 100, respiratory rate 24, and blood pressure 95/70. The general physical examination was essentially negative. No masses could be felt in the abdomen and there was no abdominal tenderness. The erythrocyte count was 3.2 million, the leucocyte count was 7,250, and the hemoglobin was 9.7 grams per 100 c.c. of blood. A serologic test for syphilis was negative. Examination of the urine was not remarkable.

During his period of hospitalization he had no further gross bleeding and no abdominal pain. On fluoroscopic examination no abnormalities were seen in the stomach. There was a slight deformity at the junction of the first and second portions of the duodenum. The roentgenologist thought that this finding was suggestive of duodenal ulcer. An exploratory laparotomy was decided upon and he was prepared for operation by four transfusions of whole blood, with a resultant rise of the erythrocyte count to 4.0 million and of the hemoglobin to 10.8 grams. At operation (A.E.G.) on December 19, an area 1.0 cm. in diameter was noted in the serosa on the anterior wall of the duodenum which was suggestive of an ulcer. A subtotal gastrectomy was performed. This was of the Polya type and included the abnormal area of the duodenum. Examination of the portion of stomach and duodenum removed failed to show any lesion. The postoperative course was uneventful and he was discharged from the hospital on Dec. 31, 1945.

He was readmitted to the hospital on Jan. 6, 1946. For the preceding three days he had had severe, generalized, cramping abdominal pains. On examination, there was no evidence of shock. The abdomen was diffusely tender but was not rigid. There were normal peristaltic sounds. The erythrocyte count was 3.88 million and the hemoglobin was 9.4 grams.

Severe abdominal pain persisted for three days and required repeated injections of morphine for its relief. On the third hospital day he vomited a small amount of bright red blood, and following this had tarry stools. In spite of three transfusions of 500 c.c. of blood, his erythrocyte count fell to 3.0 million and his hemoglobin to 7.7 grams. On the eighth hospital day he again had severe cramping abdominal pain and vomited a large amount of dark blood containing clots. During the remainder of his hospital stay until death he had almost continuous, and very severe abdominal pain and repeated hematemeses. A Jutte tube was inserted and the stomach was irrigated with warm physiologic saline solution. Whenever the tube was unclamped dark clotted blood poured from it under considerable pressure. Four more transfusions were given but he grew gradually worse and died in shock on Jan. 18, 1946.

Fig. 1.—The esophagus, stomach, and aorta viewed from their posterior aspect. The aorta has been opened. The arrow points to the point of rupture of the aorta, near the origin of the celiac axis. The aneurysmal sac lies anterior to the aorta and is hidden by it in this photograph. *OE*, esophagus; *ST*, stomach.

Autopsy Findings.—An autopsy (40109-S) was performed (E. S. M.) one hour after death. The body was that of a well-developed and well-nourished white man. There was a recent, healed surgical wound in the right hypochondrium, but no other gross abnormalities were seen in the skin or subcutaneous structures. The peritoneum was smooth and glistening, showing no evidence of old or recent inflammation. The surgical wounds involving the stomach were healed. The

stomach was distended with a huge blood clot which extended into the jejunum and esophagus. No ulcer could be found in the duodenal mucosa or in the gastrojejunostomy margin.

On the posterior wall of the stomach, 2.0 cm. below the esophageal ostium, there was an opening in the mucosa measuring 7.0 mm. in diameter. Immediately adjacent to this were two smaller openings in the mucosa. These three openings were plugged with fibrin. A probe could easily be passed through these into an aneurysm measuring 3.0 cm. in diameter. The aneurysm was adherent to the posterior wall of the stomach and to the anterior surface of the aorta. An opening, 6.0 mm. in diameter, connected the lumen of the aorta with that of the aneurysmal sac. The opening in the aorta was slightly to the left and immediately above the beginning of the celiac axis. The intima of the aorta was smooth, showing very little atherosis. The aneurysm was partially filled with a laminated thrombus which was not fixed to the wall. The wall of the aneurysm measured from 3.0 to 5.0 mm. in thickness. Several small but firm lymph nodes were found in the retroperitoneal tissues surrounding the aneurysm. The findings in the aorta and stomach are shown in Figs. 1, 2, 3, and 4.

Fig. 2.—The segment of aorta has been retracted downward to reveal the aneurysmal sac (arrow) lying anterior to it. *OE*, esophagus; *ST*, stomach.

The spleen, liver, adrenals, and kidneys showed no gross lesions. The pleurae were smooth, and the lungs were dry and air containing. Old scars and emphysematous blebs distorted the apex of each lung. At the bifurcation of the trachea there was a caseous node, measuring 15 mm. in diameter. The heart was normal.

Sections from the aortic wall, the aneurysmal sac, and the stomach showed that this was a false aneurysm resulting from destruction of the aortic wall by tuberculous granulation tissue. Sections from the wall of the aorta at the opening into the aneurysm showed necrosis of the wall, with little demonstrable inflammatory changes except in the adventitia where there was tuberculous granulation tissue merging into similar tissue forming the inner wall of the aneurysmal sac. No aortic tissue could be recognized in the wall of the sac. Beyond this area of tuberculous tissue there was lymphocytic infiltration containing moderate numbers of plasma cells and eosinophilic

Fig. 3.—The stomach, opened along its greater curvature. The point of erosion of the aneurysm into the stomach is indicated by the arrow. The gastrojejunal anastomosis is in the shadowed area in the lower portion of the stomach and is not shown clearly in this photograph.

granulocytes. The outer layer of the sac was composed of fibrous connective tissue in which there were many small blood vessels. Sections from the wall of the aneurysm at its opening into the stomach showed tuberculous granulation tissue involving all of the layers of the stomach wall. No acid-fast bacilli were demonstrated in sections of the aneurysmal sac. Miliary tubercles, some with caseous centers and Langhans' giant cells, were found in the lymph nodes near the aneurysm, in the liver, and in the spleen. The large caseous node in the mediastinum showed active tuberculous inflammation. Sections from the scars in the apices of the lungs showed fibrosis but no tuberculous tissue. No other significant lesions were found.

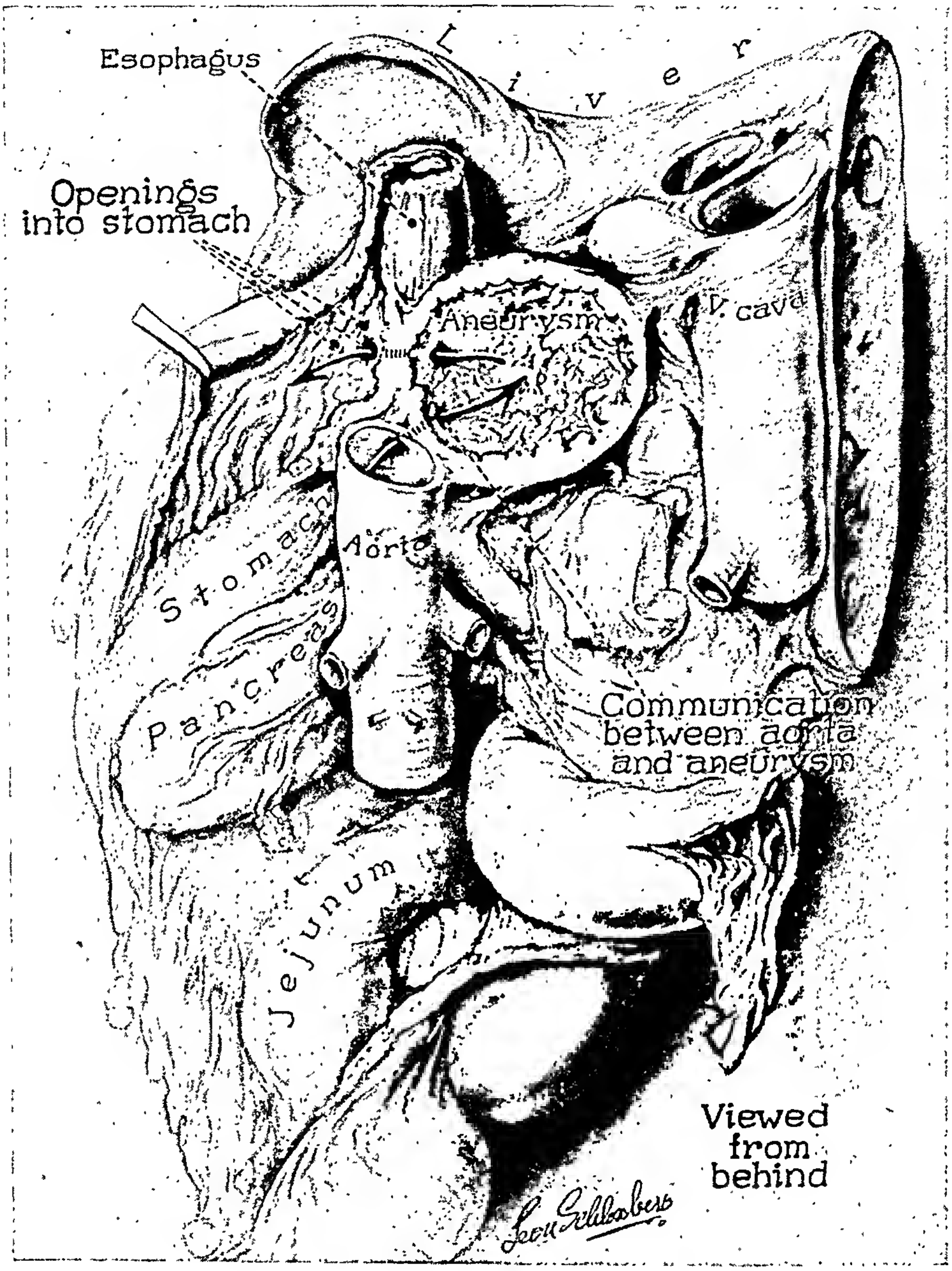

Fig. 4.—A drawing of the stomach, central portion of the liver, a segment of the aorta, and the aneurysmal sac, removed en bloc and viewed from the posterior aspect.

DISCUSSION

Although the apical scars showed fibrosis only and no tuberculous inflammation was demonstrated on microscopic examination, it may be assumed that the bilateral, scarred areas in the lung apices were healed tuberculous lesions; that the caseous tracheobronchial node resulted from tuberculous pulmonary lesions; that tissue, presumably a lymph node, lying between the aorta and the stomach was then involved with tuberculosis (though the course of this invasion is not explained); that the tuberculous process in this area extended into the walls of the aorta and of the stomach; that when the muscular coat of the aorta was

destroyed, there was massive hemorrhage expanding this tissue into a false aneurysmal sac; and that rupture then occurred through the weakest point, which was the adherent stomach wall. It is interesting to speculate on the role of the two smaller openings of the aneurysmal sac into the stomach and whether the hematemeses eight weeks and five weeks, respectively, before death were from these. There were three episodes of hemorrhage and three openings, all of which were plugged with fibrin at the time of death.

The miliary tubercles in the neighboring nodes, in the liver, and in the spleen are thought to have come from hematogenous spread from the tuberculous infiltration of the aortic wall, the latter the result of extension of the process from the adjacent tuberculous tissue and not itself hematogenous. The only two instances of the last named type of incidence that we have been able to find are the cases of Owens and Bass[1] and of Brooks and Dawson,[2] which have been cited.

SUMMARY

1. The twenty-three reported cases of tuberculous aneurysm of the abdominal aorta have been reviewed briefly.

2. The forty-one reported instances of rupture of an aneurysm of the abdominal aorta into the gastrointestinal tract, five of these into the stomach, have also been reviewed and three cases from the literature have been added.

3. These have been tabulated serially with those of Rottino[4] and of Hunt and Weller.[5]

4. A case of tuberculous aneurysm of the abdominal aorta which ruptured into the stomach has been reported. An aneurysm of this type with rupture at this site seems to be unique in medical literature.

Since this report was accepted, there has come to the attention of the authors the article of Dr. R. B. Pomerantz (Am. Heart J. 37:142, 1949) in which he referred to two additional cases of rupture into the jejunum (one of his own), and one case of rupture into the stomach.

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Abstracts and Reviews

Selected Abstracts

Ramos, J. G., Mendez, R., and Rosenblueth, A.: Studies of Flutter and Fibrillation. VI. Effects of Acetylcholine and Epinephrine on the Ventricular Muscle of Mammalians. Arch. Inst. Cardiol. de Mexico **18**:301, 1948.

The effects of acetylcholine and epinephrine on the ventricle of cats were studied under Dial anesthesia after exposure and denervation of the heart and ligation of the adrenal glands. The results thus obtained were confirmed on heart-lung preparations in dogs.

Ventricular fibrillation was induced by acetylcholine, small doses of epinephrine, potassium chloride, and by block of some of the capillaries following the injection of talcum powder or air.

Fibrillation rarely stopped spontaneously, but it could be interrupted by injection of large doses of epinephrine (0.1 to 0.3 mg.) and by massage. Fibrillation always ended simultaneously in all points of the ventricle. The most frequent mode of termination was transformation of fibrillation into flutter, which was followed by reversion to normal rhythm.

The discussion emphasizes the significant difference existing between ventricular, auricular, and nodal tissues in regard to the action of acetylcholine. The action of the latter does not require nerve endings and is effected without other chemical mediation.

The theory that fibrillatory activity presents continuous random waves is supported by the present study.

LUISADA.

Massias, C.: Ortner's Syndrome in the Course of Mitral Stenosis. Arch. d. mal. du coeur **41**:261, 1948.

The author reports a case of mitral stenosis and discusses the causes and frequency of this uncommon syndrome. Although Ortner believed that paralysis of the left recurrent laryngeal nerve resulted from compression of the dilated left auricle, subsequent workers have stated that it was the result of either compression by the dilated pulmonary artery or neuritis.

Since in this reported case, the paralysis disappeared after digitalization, the author believed that the explanation of Ortner was the correct one for his case.

LUISADA.

Cappa, A., and Sanero, F.: Intravenous Recorcaine in Therapy. Clin. Nuova (Rome) **6**:29, 1948.

The studies of Leriche demonstrated the sympatholytic action of procaine when injected intra-arterially. Since this demonstration, the drug has been applied in a number of conditions.

The author has used a preparation of procaine (Recorcaine) in bronchial asthma, Ménière's syndrome, anuria of glomerulonephritis, urticaria, and thromboangiitis obliterans. The dose used by the author was 1.0 Gm. of procaine dissolved in 1,000 c.c. of physiologic salt solution and injected by the drip method over a period of from sixty to eighty minutes.

The results have been extremely favorable. No disturbance followed the treatment.

LUISADA.

Allen, W. J.: The Action of Adrenaline, Ephedrine and Methedrine on the Circulation in Man. Clin. Sc. 6:269 (Jan.), 1948.

The effects of intramuscular injections of adrenaline, ephedrine, and Methedrine on the rate of blood flow in the human forearm and hand have been investigated by the use of the venous occlusion plethysmograph.

Adrenaline, when given intramuscularly in doses of 1.0 mg., acted rapidly, effects being conspicuous within one and one-half to two minutes, and maximum five minutes after completion of the injection. Strong palpitation, tremor, epigastric discomfort, apprehension, and sometimes headache or fullness of the head were invariably produced by this dose of adrenaline. Pallor was marked. After subcutaneous injection, the effects began later and were less intense. Following intramuscular injection the severe subjective symptoms usually lasted no longer than ten minutes, after which they became relatively mild, whereas the circulatory effects persisted for a considerable time. Tremor was the most persistent manifestation. The heart rate was only slightly and variably affected, averaging an increase of 10 beats per minute. Blood flow in the forearm also showed wide variation from case to case, but an increase was always produced. In seven cases the flow rose to an average of two and one-half times its resting value. One hour after the injection the blood pressure had begun to fall, the heart rate and forearm flow were still elevated, and palpitation and tremor persisted.

Ordinary intramuscular doses of adrenaline raise the systolic blood pressure, lower the diastolic or leave it unchanged, accelerate the heart to a small degree, and cause a considerable increase in the blood flow in the forearm.

In a similar series of experiments intramuscular injections of 60 mg. and 90 mg. of ephedrine hydrochloride were used. The action of the substance began later than that of adrenaline, and the full effect was not attained until thirty minutes after administration. Some palpitation was always produced. The action of the drug extended over several hours. Changes in heart rate were small and irregular, the composite analysis showing that the larger dose produced a protracted decrease of about 10 beats a minute. As in the case of adrenaline, the forearm blood flow varied irregularly but was always increased, though to a smaller extent than when adrenaline was used

Thus, intramuscular doses of 60 mg. and 90 mg. ephedrine hydrochloride differ in effect from those of 1.0 mg. adrenaline in that the systolic pressure is usually more greatly increased, the diastolic pressure is either raised or unchanged, and is scarcely ever lowered, the heart tends to be slowed rather than quickened, and the forearm blood flow is increased to a smaller extent than when adrenaline is used.

The dose of Methedrine used was 20 mg. in each case. The heart rate varied in an unpredictable manner but tended to show a certain parallelism with the blood flow in the forearm which was increased in all cases to a very variable degree, both from one subject to another and in each subject during the course of each experiment.

An intramuscular injection of 0.5 mg. adrenaline, after intravenous atropine, had a temporarily greater pressor effect than 1.0 mg. adrenaline alone, and the heart rate remained at the high level of 125 per minute induced by atropine. Adrenaline alone increased the blood flow in the forearm from 2.0 to 6.0 c.c. per minute. Atropine increased the flow from 2.0 to 4.0 c.c. and an additional injection of 0.5 mg. adrenaline further raised the flow to nearly 10 c.c. per minute.

Injection of 90 mg. ephedrine hydrochloride produced a rather greater rise of arterial pressure, particularly diastolic, when preceded by atropine than when given alone. Whereas ephedrine used alone slowed the heart, it quickened the rate greatly after atropine. As in the case of adrenaline, the forearm blood flow was increased over and above the small rise which followed the intramuscular injection of atropine.

When Methedrine was tested, subjects were chosen who had shown a protracted slowing of the heart after a 20 mg. dose. Atropine affected the response to Methedrine in the same way that it did the response to ephedrine. The pressor effects, both systolic and diastolic, were increased, the heart rate rose rather than fell, and the forearm blood flow increased.

In man, adrenaline, ephedrine, and Methedrine, acting directly on the heart, all tend to accelerate the rate, but in most individuals the vagus tone is sufficient to permit only a small increase in rate or to produce an actual slowing. Atropine in 2.0 mg. doses effectively removes this restraint.

The response of blood flow to intramuscular adrenaline after sympathectomy was essentially the same as in the normal forearm. This was also the case with ephedrine. This suggests the action is largely peripheral. All of these substances seem to be able to bring about an active dilatation of the blood vessels in skeletal muscle, but, as with the action on the skin, adrenaline is the most effective.

Doses of adrenaline and ephedrine increase the cardiac output and apparently decrease the total peripheral resistance, adrenaline producing the larger effect in both instances. The results here described suggest that skeletal muscle is probably the main site of this decreased resistance. The greater dilatation observed with adrenaline than with ephedrine agrees with the greater decrease in total peripheral resistance after adrenaline and is probably a factor in the lowering of diastolic pressure by adrenaline, while ephedrine raises it. In general, the results show a very ready dilatation of muscle vessels by adrenaline, a much smaller dilatation by Methedrine, and an intermediate action by ephedrine.

These substances in those doses, which strongly dilate muscle vessels, lead to a considerable lowering of peripheral resistance and allow some acceleration of the heart, while no acceleration, or actual slowing, is found when the muscle dilatation is small. In general, the diastolic blood pressure is normal or low when muscle flow is high, and vice versa.

BELLET.

Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Low Blood Pressure in Diabetic Coma. Clin. Sci. 6:247 (No. 4), 1948.

It has long been recognized that in the later phases of diabetic coma the blood pressure may fall to low levels, and that this change is often irreversible, death following within a few hours. Efforts to raise the arterial pressure by drugs have been on the whole unsuccessful, while large intravenous infusions, given in the belief that the falling blood pressure was due to a diminished blood volume and a decreasing cardiac output, have frequently resulted in pulmonary edema.

The low blood pressure in diabetic coma is due to a decreased total peripheral resistance, which is below 50 per cent of the normal value. The site of the vasodilatation has not been determined. The cool, pale skin suggests that skin blood flow is diminished. Attempts to combat the peripheral vasodilatation by constrictor drugs have so far failed. The vasoconstrictor drugs, pitressin, digitalis, and d-N-methyl amphetamine hydrochloride (Methedrine), fail to raise the low arterial pressure, or show only a small transient effect. The vessels may show a transient initial constriction, but then appear to become insensitive to further injection of the drugs.

BELLET.

Cohen, S. M., Edholm, O. G., Howarth, S., McMichael, J., and Sharpey-Schafer, E. P.: Cardiac Output and Peripheral Blood Flow in Arteriovenous Aneurysm. Clin. Sci. 7:35 (No. 1), 1948.

The observations were made on twelve patients. All were men and all had been wounded less than two years previously except two, Case 10, who had been wounded five year years before, and Case 12, whose aneurysm had been present for twenty-nine years.

Cardiac output and right auricular pressure were studied by the technique of cardiac catheterization. Blood flow was measured in the forearm and in the leg by means of a venous occlusion plethysmograph. The arm was immersed in a water bath at 34° C., while the leg was in air at room temperature. Circulation through the aneurysm was shut off by digital pressure proximal to the aneurysm. In order to allow time for the circulation to reach a steady state, closure was maintained for one minute before the right auricular samples were withdrawn. Blood flow changes in the limbs were recorded within thirty seconds of closure of the shunt.

Cardiac output in liters per minute per 100 c.c. oxygen consumed was increased above the normal average of 2.2 in nearly all cases, the highest figure being 4.5 in a patient with a very large aneurysm. The venous filling pressure and heart rate were moderately increased. The increased cardiac output in large arteriovenous aneurysms has some relationship to the size of the communication. Closing the arteriovenous fistula by compressing the artery proximal to the shunt pro-

duced slowing of the heart rate, increase in the diastolic blood pressure, a considerable decrease in cardiac output, and a small decrease in right auricular pressure. In large shunts neither cardiac output nor right auricular pressure fell to normal levels on closure.

Two milligrams of atropine, intravenously, increased cardiac output to high levels, but changes in rate, cardiac putput, and auricular pressure were still produced by temporary closure of the shunt. Output changes on closure are more related to heart rate than to filling pressure changes.

The blood flow in limbs unaffected by the shunt was within normal limits and showed a conspicuous increase on closure of the shunt. This increase was greatly reduced by procaine block of the mixed nerves to the limb, suggesting that the increased flow was mainly due to vasodilatation and only in part produced by the rise in mean blood pressure. Blood flow in the affected limb distal to the arteriovenous fistula was reduced in lesions which had been present up to two years, was normal in lesions present up to five years, and conspicuously was increased in a lesion of twenty-nine years' duration. The flows recorded after compression of the artery proximal to the fistula suggested that in early lesions most of the blood entering the distal part of the limb traverses the aneurysm, while in long-standing lesions much arrives through other arterial channels. Resting blood flow in a limb one month after quadruple ligature was the same as in the normal contralateral limb and the vascular responses to raising body temperature were identical.

BELLET.

Lewis, J. H., and Ferguson J. H.: Thrombin Formation. I. The Role of Calcium, Serum AC-Globulin and Tissue Thromboplastin. J. Clin. Investigation 6:778, 1948.

These investigators studied the clotting time in vitro of blood to which had been added in varying amounts prothrombin, serum accelerator-globulin (ac-globulin), tissue thromboplastin, thrombin, and fibrinogen. They concluded that the four substances, prothrombin, serum accelerator-globulin, thromboplastin, and calcium, are necessary for thrombin formation and that the yield of thrombin depends on the proportions of these substances. It was shown first that a thrombin yield is directly dependent on calcium concentration; second, that accelerator-globulin increased both the rate of formation and the yield of thrombin from a given amount of prothrombin, thromboplastin, and calcium, and, therefore that accelerator-globulin was necessary for the formation of any thrombin. Thromboplastin exerted effects similar to calcium and accelerator-globulin; without tissue thromboplastin no thrombin was formed. It is concluded that thrombin yield, as well as a rate of formation, is dependent on the quantity of each of these four reagents.

WAIFE.

Carrillo, E. G.: Comments on Two Rare Diseases in Costa Rica. Rev. argent. de cardiol. 15:112, 1948.

The authors state that both myocardial infarction and subacute bacterial endocarditis are rare in Costa Rica. Out of 8,000 autopsies, myocardial infarction was found in only 0.2 per cent and subacute bacterial endocarditis in only 2.7 per cent.

The rare occurrence of infarction is explained by the low-fat, low-calorie diet of the poor population, in conjunction with the mild climate. The rare occurrence of the bacterial endocarditis is attributed to an immunity established at a young age on account of extremely common local focal infections.

LUISADA.

Webster, B., and Reader, G. G.: The Effect of Antisyphilitic Treatment on the Microscopic Appearance of Syphilitic Aortitis. Am. J. Syph., Gonor., & Ven. Dis. 32:19 (Jan.), 1948.

Microscopic sections of the aortas of forty-five patients with gross evidence of syphilitic aortitis at post-mortem examination in whom clinical data were available were studied to determine the effect of treatment on the microscopic picture of syphilitic aortitis. The patients were

divided into three groups according to whether they had received "adequate" treatment, "inadequate" treatment, or no treatment.

Nineteen patients had been adequately treated with approximately twenty or more arsenical and twenty or more bismuth injections. Another nineteen patients had received no treatment or such a negligible amount that it could not conceivably have affected the course of their disease. All of the untreated patients showed an active syphilitic process. Only three of the adequately treated patients, on the other hand, showed active inflammation, although one other patient, whose aorta showed minimal cellular reaction, exhibited some endarteritis. Of the patients who had received inadequate treatment, five of the seven showed activity of the syphilitic inflammatory process. Eighteen patients among the forty-five investigated (or 40 per cent) gave a history of primary or secondary syphilis or had been diagnosed as latent syphilis a known number of years before death. No correlation was demonstrable between duration of infection and activity of aortitis. In ten of nineteen of the untreated patients and seven of nineteen of the adequately treated patients, syphilitic aortitis, valvulitis, or aneurysm was the cause of death. Only three patients in this series received penicillin as part of their therapy. Two of these showed an inactive aortitis while the third received penicillin such a short time before death that alteration of the pathologic picture could not be expected.

In conclusion, the authors found that only three of nineteen patients who had received adequate treatment showed an active type of syphilitic aortitis, while all of nineteen untreated patients showed active cellular infiltration of the aorta.

BELLET.

Stryker, W. A.: Traumatic Saccular Aneurysm of the Thoracic Aorta. Am. J. Clin. Path. 18:152 (Feb.), 1948.

The author describes a saccular aneurysm of the thoracic aorta in an 18-year-old girl which followed an automobile accident in which there was injury to the chest. Death occurred six months later. Necropsy revealed subacute bacterial endaortitis in the aneurysm and, in addition, organizing fibrinous pericarditis, chronic purulent interstitial myocarditis, and verrucous mitral and aortic valvulitis. Incomplete tears of the aorta following trauma are described in two other patients.

KLINE.

Rosenbaum, H., and Linn, H. J.: Tuberculoma of the Myocardium in a Patient With Tuberculous Meningitis Treated With Streptomycin. Am. J. Clin. Path. 18:162 (Feb.), 1948.

The case reported is that of a 21-year-old white man with pulmonary tuberculosis complicated by tuberculous meningitis. He was given 171 Gm. of streptomycin intramuscularly and intrathecally over a period of two and one-half months without beneficial effect. No significant cardiac alterations were noted except a sinus tachycardia and a gradual fall in blood pressure during the last days of life. At post-mortem examination the heart weighed 180 grams. A tuberculoma was present in the interauricular septum which projected into the right auricle.

The incidence, etiology, and pathogenesis of the lesion are briefly discussed.

KLINE.

Garrey, W. E., and Townsend, S. E.: Neural Response and Reactions of the Heart of a Human Embryo. Am. J. Physiol. 152:219 (Feb.), 1948.

The sinus, atrium, and two ventricular portions of the heart of a human embryo of approximately 13 weeks of fertilization age were examined for the effect of temperature and vagal stimulation on automaticity and contractility. The heart of this 100 mm. embryo was rapidly chilled in Ringer's solution (5°C.) and then gradually warmed for the experimental periods. The heart could be kept beating for hours.

Acetylcholine bromide in concentration up to 1:10,000 had no inhibiting effects on the ventricles and only a slight and delayed inhibitory effect of the sinus-atrium preparation. The sinus

preparation beat at all temperatures between 10° and 40°, with an intrinsic rate of 157 at 37° centigrade. This rate approximates that of adult mammalian hearts when free of nervous regulation. It is assumed that the inhibitory function of cardiac nerves is a late fetal development.

HECHT.

Kremer, W. F.: Blood Pressure Changes in Response to Electrical and Chemical (Acetylbetamethylcholine) Stimulation of the Cerebral Cortex in Dogs. Am. J. Physiol. 152:314 (Feb.), 1948.

In eleven dogs under sodium amytal or Dial anesthesia, electrical or chemical stimulation of certain areas of the brain evoked a fall in systolic and diastolic blood pressures. Two particularly responsive areas were found that evoked a profound fall in pressure when brought in contact with a small amount of 2.5 per cent solution of acetyl-beta-methylcholine. These two areas were the posterior sigmoid gyrus near the midline and the anterior ectosylvian gyrus. This action was conspicuously prolonged when these regions were pretreated with prostigmine salicylate powder. Local application of acetyl-beta-methylcholine appeared superior in action, lasted longer, and was confined to more circumscribed regions than the usual faradic stimulation.

HECHT.

Goodale, W. T., Lubin, M., Eckenhoff, J. E., Hafkenschiel, J. H., and Banfield, W. G., Jr.: Coronary Sinus Catheterization for Studying Coronary Blood Flow and Myocardial Metabolism. Am. J. Physiol. 152:340 (Feb.), 1948.

A slightly modified Cournand catheter was inserted through the external jugular vein into the auricles of forty-five dogs. The catheter was allowed to slip into the inferior vena cava and then was gently withdrawn. The tip was turned and shifted slightly anteromedially. In this position the tip of the catheter pointed directly toward the coronary sinus ostium and when thrust forward, entered the sinus by rounding a sharp initial bend. The position of the sinus and the contributory veins was clearly visualized by retrograde injection of Diodrast. All manipulations were performed on the anesthetized animal under fluoroscopic control and in the right anterior oblique position.

Coronary venous blood revealed extremely low oxygen saturation with an average of 4.1 volumes per cent (22 per cent saturation). Extremely high coronary arteriovenous differences were likewise found for blood lactate and pyruvate, indicating a high rate of myocardial utilization. Glucose was removed by the heart in relatively small amounts.

Autopsy studies revealed a high incidence of endocardial damage; only three of 28 dogs were found to be free of evidence of catheter injury. These consisted of small subendocardial hemorrhages and mural thrombi. The lesions occurred along the insertion of the catheter including the tricuspid and the pulmonary valves. If the catheter was inserted deep into the coronary sinus, lesions secondary to obstruction of venous outflow occurred, with gross myocardial hemorrhages in regions drained by the great cardiac veins. Standard lead electrocardiograms revealed alterations of RS-T segment and of the T wave suggesting subepicardial injury which could be demonstrated in two examples at autopsy. The injuries peculiar to deep coronary sinus catheterization may be avoided if the catheter is inserted not more than two cm. into the coronary sinus. Bursts of extrasystoles were frequently noted when the catheter touched ventricular muscle just beyond the tricuspid valve or the regions below the pulmonary conus. Cardiac catheterization may be considered a safe procedure only if definite precautions are observed.

HECHT.

Eckenhoff, J. E., Hafkenschiel, J. H., Harmel, M. H., Goodale, W. T., Lubin, M., Bing, R. J., and Kety, S. S.: Measurement of Coronary Blood Flow by the Nitrous Oxide Method. Am. J. Physiol. 152:356 (Feb.), 1948.

Simultaneous determination of coronary blood flow by the use of a bubble flowmeter and by direct sampling of blood from the coronary sinus either by direct canalization or by sampling through a cardiac catheter was performed in dogs with nitrous oxide as the tracer agent. Blood flow was calculated as flow per 100 grams of myocardium drained on the basis of nitrous oxide

concentration in coronary venous blood and in arterial blood over a ten-minute period of gas inhalation. Values of 63.7 ml. per 100 grams of tissue were obtained by the bubble flowmeter technique, 67.8 ml. per 100 grams by direct canalization. Blood samples obtained by venous catheterization revealed values of 71.3 ml. per 100 grams of tissue. The slightly higher values by the indirect method may be the result of contamination by noncoronary venous blood.

HECHT.

Riley, R. L., Himmelstein, A., Motley, H. L., Weiner, H. M., and Cournand, A.: Studies of the Pulmonary Circulation at Rest and During Exercise in Normal Individuals and in Patients With Chronic Pulmonary Disease. Am. J. Physiol. **152**:372 (Feb.), 1948.

Measurements of cardiac output and pulmonary arterial pressures were recorded by the catheter method during rest and exercise in three normal subjects and in eight patients with a variety of pulmonary diseases. In the normal group mean pressure in the pulmonary artery and vascular resistance in the lungs fell and the work of the right ventricle rose insignificantly. In patients with chronic pulmonary disease the expansibility of the pulmonary bed during exercise was limited, as demonstrated by a significant rise in pulmonary artery pressures on exercise. The work of the right ventricle was invariably higher than in normal subjects on a corresponding work level.

HECHT.

Wolff, L., and Sagall, E. S.: Intravenous Administration of Mercurial Diuretics in Man; Immediate Effect on the Electrocardiogram. Arch. Int. Med. **81**:137 (Feb.), 1948.

Three hundred nineteen intravenous injections of three different mercurial diuretic preparations were administered to 137 patients. Of these, 121 were suffering from chronic congestive heart failure, seven from cirrhosis of the liver, six from the nephrotic stage of chronic glomerulonephritis, and three from thyrotoxicosis. An initial four-lead electrocardiogram was taken on each of the patients, but during the study only Lead II was employed. The electrocardiographic pattern was recorded continuously during the period of the administration of the drug and at one-, two-, three-, and four-minute intervals after completion of the injections.

Significant electrocardiographic abnormalities were seen after thirty-six (11 per cent) of the 319 injections. Of the 137 patients investigated, twenty-seven (20 per cent) showed significant changes in the electrocardiogram. The type of disease present seemed to play no role in the incidence of abnormalities, nor did the type of mercurial used. The results did not differ in the two sexes. The abnormalities found were auricular premature beats seven times and ventricular premature beats twenty-six times. In two cases, both auricular and ventricular, ectopic beats were found. In five cases the ventricular premature beats arose from different foci. Paroxysmal ventricular tachycardia occurred on one occasion.

This study shows that there is a preponderance of ventricular abnormalities suggesting that the ventricle is more susceptible to the action of mercury than is the auricle. Further, the cardiac mechanism prior to injection does not affect the incidence of electrocardiographic abnormalities induced by the drug, with the possible exception of auricular premature beats. Untoward reactions occur even though previous injections were uneventful, and vice versa. Digitalis does not predispose to the production of arrhythmias after the intravenous injection of mercurial diuretics.

BERNSTEIN.

Liljestrand, G.: Regulation of Pulmonary Arterial Blood Pressure. Arch. Int. Med. **81**:162 (Feb.), 1948.

The author used anesthetized cats in which a special cannula was inserted in the pulmonary artery in such a way that the wall was gripped between two flanges and connected with a vertical glass tube and piston recorder. The thorax was closed so that spontaneous respiration was established in most cases.

Epinephrine in doses of 0.005 to 0.02 mg. and ergotamine, 0.3 mg., had a direct effect on the vessels of the pulmonary tree. Nervous mechanisms could not be demonstrated to affect pulmonary arterial pressure. Carbon dioxide produced small increases in pressure which remained after vagotomy, but could be abolished or reversed by ergotamine. Oxygen want produced a rise in pulmonary arterial pressure, whereas oxygen inhalation resulted in a drop. These effects were produced by variations in the degree of contraction of the arterioles and precapillaries of the lungs. The effect is not abolished by vagotomy or extirpation of the stellate ganglions or by the administration of ergotamine, dihydroergotamine, atropine, or yohimbine. The author feels that since it is a local effect, it is possibly based upon the degree of oxygenation of the venous blood in the arterioles of the lungs.

Though increase of carbon dioxide and decrease of oxygen both act to raise the arterial pressure, the effect of oxygen want is much stronger. The author concludes, therefore, that oxygen want which leads to vasodilatation in the systemic circulation acts in the opposite way in the pulmonary circulation, thereby directing blood away from badly ventilated parts of the lung to those parts which have better oxygenation. He further feels that the decrease in vital capacity after the inhalation of oxygen is produced at least in part by the dilatation of the vessels of the lung. He also believes that since anoxia increases the arterial and precapillary pressure in the lungs, the slowing of the circulation may lead to oxygen want without causing back pressure and may therefore be an important factor in the production of edema.

The author attempts to explain some of the toxic effects of oxygen on the basis of these experiments and states that the hyperemia caused by the inhalation of 100 per cent oxygen at a pressure of one atmosphere is simply the result of the physiologic dilating effect of oxygen on the arterioles and precapillaries. The edema which results is caused by the inability of the lymph vessels of the lung to carry off fluid from the lungs because of their compression by the widened arterioles and precapillaries. The disturbance of the balance between formation and removal of the lymph will result in edema.

BERNSTEIN.

Glomset, D. J., and Birge, R. F.: Morphologic Study of the Cardiac Conduction System; the Pathogenesis of Heart Block and Bundle Branch Block. Arch. Path., 45:135 (Feb.), 1948.

The authors review the history of the development of the current conceptions of heart block and bundle branch block, recalling the result of previous investigators who have known that bundle branch block can result from injury to the interventricular septum. They believe, however, that the cause of this disturbance is in the septal myocardium and not in the bundle of His or its main subdivisions.

The authors are guided by Glomset's previous studies, reiterated in the present report, showing that the bundle of His does not exist in the human being; that what has been described as the bundle of His is nothing more than a small fasciculus of ordinary cardiac muscle devoid of significance, which extends up from the ventricular septum into the auriculoventricular ring.

They conclude that heart block and bundle branch block have no basis in the pathologic disturbances of a conduction system, inasmuch as the latter hardly exists in the human heart. They believe that these lesions, heart block and bundle branch block, develop on the basis of damage to the upper part of the ventricular septum. They also conclude that Purkinje fibers, while they exist in human hearts, have in reality little or no differentiating structural development, their apparent characteristic morphology being due to post-mortem degeneration; that their reputed glycogen content is nonexistent, and their swollen appearance, a mechanical artefact.

The authors analyze the pathologic data in fifty-eight cases of heart block and bundle branch block drawn from the literature, and twenty-one cases personally studied. They believe that replacement fibrosis secondary to arteriosclerosis in the upper part of the ventricular septum is the important cause of what has hitherto been considered conduction system pathology. It is difficult to find a preponderance of this damage on one or the other side of the septum; rather, in their opinion, it is diffuse in the majority of cases. Therefore, they believe that in bundle

branch block the electrocardiographic pattern is determined by the pre-existing preponderance brought about by the underlying etiological factors.

The authors emphasize that in A-V heart block, in "90 per cent of the recorded cases, a considerable portion of the septal myocardium had been destroyed"; likewise, a high percentage of the various types of bundle branch block showed a similar lesion. When an infarct occurred in the upper part of the septum, the right coronary artery was almost always the site of occlusion. Conversely, 10 per cent of the cases of heart block and 20 to 30 per cent of the cases of bundle branch block did not show any morbid changes in the ventricular septum. It is pointed out that in such cases the rich intrinsic nervous system comprising numerous ganglia in the atria may be at fault and responsible either in a primary or in an accessory manner for heart block and bundle branch block.

GOULEY.

Will, O. A., Jr., Rehfeldt, F. C., and Neumann, M. A.: A Fatality in Electroshock Therapy. J. Nerv. & Ment. Dis. **107**:105 (Feb.), 1948.

The authors review thirty-three fatalities following electroshock therapy which they have collected from the literature and record one case of their own.

The initial treatment in the authors' case was uneventful and two days later a second was given, with 6 c.c. of curare being given intravenously. A grand mal attack occurred. About five minutes after the cessation of the convulsion, generalized muscular twitchings were noted and the patient suddently ceased breathing. The patient showed no spontaneous response to the artificial respiration. The heart beat was audible for at least fifteen minutes after the cessation of respiration.

Clinically the death seemed to be the result of respiratory failure and it was thought that the cause might have been damage to medullary centers by the electric current or by changes in the blood and intracranial pressures.

At necropsy the brain was swollen, the convolutions were flattened, and the meningeal coverings were dry. Only 25 c.c. of intracranial fluid was collected during the removal of the brain. Arteries at the base of the brain were unusually narrow and thin walled and free from arteriosclerosis. The circulatory system gave no evidence of a disease process. The aorta was hypoplastic. The cause of death was given as acute cerebral edema and medullary compression.

BELLET.

Sirry, A.: Radiological Study of Bilharzial Cor Pulmonale. J. Roy. Egyptian M. A. **31**:146 (Feb.), 1948.

The object of this communication is to report the radiologic picture in bilharzial Ayerza's disease and its radiological differentiation from other forms of chronic cor pulmonale.

Six cases were chosen as examples of bilharzial cor pulmonale. The diagnosis in two patients was confirmed by necropsy. All patients gave a history of bilharzial infection of some years' duration, and in all, ova were found in both urine and stools. This suggests that bilharzial cor pulmonale follows a rather severe infection of bilharziasis, and is the result of long-standing arterial obstruction.

Clinically the cases presented the following features: bilharzial livers and enlarged spleens; cyanosis, in two cases, accompanied by congestive heart failure; and the clinical signs of an enlarged pulmonary artery and conus. Only one patient with a huge aneurysmal dilatation of the pulmonary artery showed a regurgitant pulmonary murmur.

The radiological study of these patients showed the following: enlargement of the pulmonary artery and conus; prominent hilar shadows; enlargement of the right ventricle and auricle; slight or no enlargement of the left side of the heart; restricted movement and elevation of the left cupola of the diaphragm; no indication in the lung fields of the lesions described as common in pulmonary bilharziasis; and normal position and size of the ascending aorta in every case. The size and position of the aorta are the most important radiologic differential signs

suggested by this study. In bilharzial cor pulmonale the ascending aorta is normal in size and position. These conditions occur in young persons in whom acquired aortic pathology is usually absent.

BELLET.

Sollmann, T., and Estable, J. J.: The Action of Procaine, Salicylate and Benzoate of Sodium on the Excitability of Skeletal Muscle and of Nerve. Anesthesiology 9:188 (March), 1948.

The authors' investigations were made on preparations of the sciatic nerve and gastrocnemius muscle of frogs, immersed in a Ringer salt solution kept near 0° centigrade.

Survival of the nerve and muscle is not prolonged by brief or continued sojourn in any concentration of procaine hydrochloride. All concentrations that have any effect at all produce progressive depression of response to stimulation and shorten the survival time. The response of muscle to direct stimulation is almost quantitatively parallel to the depression of response to nerve stimulation. The speed and degree of the depression increase with the concentration of the procaine. Reversibility by transfer to unpoisoned Ringer solution seems to depend on the concentration of procaine and the time of contact more than on the degree of depression.

As a comparative test of direct muscular depression by procaine hydrochloride, sodium salicylate, and sodium benzoate, the solutions were injected into the peripheral end of the ligated femoral artery of rabbits; the response was tested by faradic stimulation applied to the saphenous nerve and to the exposed muscles. It was seen that the three agents depress the direct muscular response equally as well as the reflex response. The potency of procaine hydrochloride is materially greater than that of sodium salicylate and sodium benzoate. The "pseudohernia" of procaine involves depression of muscle as well as nerve; indeed, the direct effect on muscle is greater than on nerve. Similar effects are produced by administration of 2 per cent sodium salicylate, but were not produced by 5 per cent sodium benzoate.

Satisfactory local anesthesia was obtained with 0.2 per cent solution of procaine hydrochloride and with 2 per cent and 5 per cent solution of sodium salicylate, but only light anesthesia resulted when a 5 per cent solution of sodium benzoate was employed. Integration of the observations suggests that sodium salicylate in 2 per cent solution could be used for injection anesthesia, but that it is materially inferior to procaine, being less potent and more irritant. The anesthetic action of sodium benzoate is demonstrable but too feeble for practical use.

The experiments with excised nerve and muscle show that the paralysis resulting from procaine hydrochloride become irreversible if the relatively high concentrations act for relatively long periods.

BELLET.

Maggioni, G. F.: Salicylate Therapy in Children. Arch. Dis. Childhood 23:40 (March), 1948.

Some observations are presented in this paper on the fate of salicylates in normal and rheumatic children. The efficacy and specificity of this therapy are not discussed. No restrictions were placed on food or liquid intake during these observations.

The intravenous administration of salicylate was not used, because this route of administration has no practical advantage. The drugs used orally in the routine treatment of rheumatic fever were (a) sodium salicylate (1 part) with sodium bicarbonate (2 parts) in a liquid mixture of which ½ ounce was said to contain 20 grains of the drug; (b) aspirin, five grains per tablet; and (c) calcium aspirin, 5 grains per tablet. Sodium salicylate in water, taken by mouth, was rapidly absorbed; its presence could be detected in blood and urine within fifteen to twenty-five minutes. The peak in the blood level was reached in from one and one-half to two hours. Thereafter the concentration decreased slowly. The quantity of salicylate that could be recovered from the urine of normal subjects after a single dose was about two-thirds of that ingested. In rheumatic patients treated continuously, the salicylate recovered in the urine was 50 or 60 per cent, or less, of the intake, especially during acute periods.

As there is a loss of vitamin C in acute rheumatic fever, there should be a supplementary administration of this vitamin to avoid depletion of ascorbic acid reserves. The giving of vitamin A in addition seems to be useful.

The authors conclude that an appropriate scheme of salicylate therapy in children with rheumatic fever should include the oral use of freshly prepared solutions of sodium salicylate in flavored water with sodium bicarbonate added in the proportion 1:1 when given every four hours, or 1:2 when given every two hours. The last dose in the evening and the first in the morning may be doubled to permit a longer undisturbed interval during the night. The administration by enema seems to be indicated in patients with severe vomiting. Aspirin or calcium aspirin in tablets can also be used. The quantity of sodium salicylate which in children raises the level to 25 or 35 mg. per 100 ml. is in the range of 0.12 to 0.18 grain per kilogram of body weight. The estimation of salicylate plasma level seems advisable to control the accuracy of the administration and to avoid overdosage.

BELLET.

Cohen, M. E., White, P. D., and Johnson, R. E.: Neurocirculatory Asthenia, Anxiety Neurosis or the Effort Syndrome. Arch. Int. Med. 81:260 (March), 1948.

An attempt is made to summarize certain major positive findings (physical, physiological, subjective, and objective) which the authors have observed in a five-year study of neurocirculatory asthenia. The confused terminology regarding this condition is discussed and the various synonyms described. The exact limits of the terms so used are not clearly defined, but they all refer to a type of disorder in which several of the following features are striking: nervousness, easy fatigue, shortness of breath, palpitation, spells of faintness, giddiness, apprehension, poor muscular work performance, and emotional stress. However, all or any of these symptoms are not associated with any diagnosable disease of the heart, lungs, nervous system, or thyroid gland.

The authors studied 144 patients with an average age of 26.9 years. Abnormal findings were few and such positive findings that were present occurred in a high percentage of cases. These findings included a high resting pulse rate, increased respiratory rate, flushed face, hyperactive knee jerks and ankle jerks, and tremors of the fingers. In contrast to these findings was the multiple nature and high incidence of subjective symptoms. Studies of muscular work demonstrated a defect in aerobic metabolism in all grades of work. Pulmonary ventilation was abnormal as was awareness of dyspnea. The pulse rate for all grades of exercise was abnormally high. Heart size, electrocardiograms, resting circulatory measurements, and cardiac output were all normal. Quantitative studies of pain revealed an abnormal reaction to painful stimuli. All patients diagnosed as having neurocirculatory asthenia were placed in the "neurosis" category on psychological testing.

Statistics revealed a definite familial incidence with an almost "Mendelian" hereditary pattern, and the authors do not believe that environment and experiences have been demonstrated to be the major factors in causing the disorder.

From a prognostic viewpoint, a convenient distinction is made, on the basis of history alone, between acute and chronic neurocirculatory asthenia. Those diagnosed as having an acute disturbance demonstrated more nearly normal observations than did patients with chronic disease. Strong emphasis is placed on the determined fact that basal measurements made with the patients resting may not show abnormalities, while measurements made with the subject under stress may show marked differences; the stronger the stress, the greater the deviation from normal. No specific effective curative measures are proposed.

BERNSTEIN.

Stead, E. A., Jr., Warren, J. V., and Brannon, E. S.: Effect of Lanatoside C on the Circulation of Patients With Congestive Failure. Arch. Int. Med. 81:282 (March), 1948.

Twenty-two patients in congestive heart failure were observed after they had received a single intravenous injection of 1.6 mg. of lanatoside C. Control observations were made on admission in all cases and repeated after the total digitalization. Cardiac output (direct Fick),

arterial pressure (femoral artery), atrial pressure, and peripheral resistance were established in all cases.

The first observed effect was an average fall in venous pressure of 62 mm. H_2O which began in five to ten minutes and continued for thirty to sixty minutes. This decrease was not preceded by diuresis and appeared independent of a decrease in the blood volume. The stroke volume improved in twenty patients, but the cardiac rate was variable. There was no constant change in oxygen consumption. The mean arterial pressure usually increased with no consistent change in diastolic pressure. The peripheral resistance fell in eighteen of twenty observations. In eighteen of the twenty-two subjects, the average increase in cardiac output was 1.6 liters per minute. The increase in output resulted primarily from a decrease in arteriovenous oxygen difference and represented an increase in blood flow to the tissues of 2,300 liters per day. Also demonstrated were the facts that patients in congestive failure may have a high cardiac output which can be further increased with digitalis and that lanatoside C increases the cardiac output in the presence of a normal rhythm.

The prime action of the digitalis appears to be on the ventricular muscle which enables the ventricles to increase their output. There is a fall in atrial pressure which is primarily due to changes in venous tone. The further fall in venous pressure which may occur later appears to be related to the decrease in blood volume caused by the diuresis.

BERNSTEIN.

Evoy, M. H., and de Takats, G.: Place of Intermittent Venous Hyperemia in the Treatment of Obliterative Vascular Disease. Arch. Int. Med. 1:292 (March), 1948.

After preliminary tests of the peripheral circulation, the patients were instructed to rent or buy an automatic rhythmic venous constrictor apparatus, to use it at home for two to three hours daily, and to report every three months for the first year, twice a year for the second year, and once in the third year. Improvement was measured by objective methods, the most sensitive of which were found to be venous filling time and walking ability. Subjective improvement was noted in a higher percentage than objective improvement, but subjective improvement without objective evidence of improvement was disregarded. Of 100 patients studied, sixty-seven derived some benefit, whereas thirty-three either showed no improvement or had a progression of the disease.

The authors conclude that intermittent venous hyperemia is contraindicated in acute venous thrombosis, lymphangitis, severe arteriolar obstruction, and frank gangrene. Sympathectomy is still the treatment of choice in those cases with definite spasm, but venous hyperemia appears to offer additional benefit after vasoconstrictor tone is abolished. Diabetic patients with peripheral nerve involvement, patients with pronounced vascular spasm, and those with arteriolar and capillary stasis are not suitable subjects. Patients with vascular sclerosis in whom preliminary tests show poor response to sympathectomy or those who have already undergone sympathectomy, but still have considerable claudication, constitute the group for whom this form of treatment is indicated. It is an ambulatory treatment to be used at home. "If the rhythmic constrictor did nothing else but supply the patient with a harmless placebo, it would fulfill a need in geriatric practice."

BERNSTEIN.

Olinger, Mervin G.: Mixed Infection in Subacute Bacterial Endocarditis. Arch. Int. Med. 81:334 (March), 1948.

Mixed infection in two cases of subacute bacterial endocarditis which responded favorably to antibiotic therapy are reported. In one case *Corynebacterium pseudodiphthericum* and *Streptococcus viridans* were present; in the second case *Streptococcus viridans* and *Hemophilus parainfluenzae* were present. The recognition of mixed infection is important in view of the present choice of antibiotics. In one case it was obvious that both streptomycin and penicillin were essential. Adequate selection of suitable antibiotics may require identification of all the organisms involved in a given infection. It is suggested that mixed infection in subacute bacterial endocarditis may be more frequent than is reported.

BERNSTEIN.

Findley, J. W., Jr., and Adams, W.: Primary Systemic Amyloidosis Simulating Constrictive Pericarditis. Arch. Int. Med. 81:342 (March), 1948.

A case of primary systemic amyloidosis is presented in which elevated venous pressure, prolonged circulation time, low pulse pressure, small cardiac movements, low electrocardiographic voltage, hepatomegaly, decreased serum albumin with a normal concentration of globulin, albuminuria, dependent edema, and ascites led to a diagnosis of contrictive pericarditis. It is not difficult to understand how the deposition of amyloid in the heart may produce a picture which simulates the syndrome produced by constrictive pericarditis. In one disease (amyloidois) there is confinement of the individual muscle fibers and in the other (constrictive pericarditis) there is confinement of the organ as a whole. One of the most interesting and unusual features of this case was the spectacular involvement of the nerves. The occurrence of steatorrhea and hypocalcemia was of interest in connection with a recent suggestion that amyloidosis may occasionally cause the sprue syndrome. Biopsy of muscle might have made the diagnosis possible in this case prior to autopsy, but in general, the authors stress the multiplicity of symptoms and the difficulty of diagnosis in the absence of a positive congo red test or certain external manifestations.

BERNSTEIN.

Strauss, H., and Greenstein, L.: The Electroencephalogram in Cerebrovascular Disease. Arch. Neurol. & Psychiat. 59:395 (March), 1948.

The authors correlate clinical signs, symptoms, and duration of illness with the type of electroencephalograms in ninety-five cases of cerebrovascular accident. The great majority of patients (sixty-seven out of ninety-five, or about 70.5 per cent) with cerebrovascular disease showed no delta activity in the electroencephalogram. A positive correlation between symptoms and signs, on the one hand, and the electroencephalogram, on the other, was found to exist in only two respects: (1) in all the patients with an electroencephalographic focus, such a focus corresponded to the anatomic site of the lesion as diagnosed on the basis of the clinical facts; and (2) all the patients with clouding of consciousness showed delta activity in the electroencephalogram. All patients with a high degree of electroencephalographic abnormality of symmetric diffuse type, asymmetric diffuse type, or parasymmetric focal type showed clinically a disturbance in the state of consciousness, whereas only some of the patients with a low degree of electroencephalographic abnormality of symmetric diffuse type or a high degree of abnormality of parasymmetric diffuse type showed a similar clinical disturbance.

Normal records were seen in patients with hemispheric lesions producing hemiparesis, aphasia, hemianopsia, and combinations of such symptoms, even though the lesions were of recent origin. In other patients similar clinical findings were associated with abnormal electroencephalograms as late as one year after the onset of symptoms. These observations show that there is no correlation between the electroencephalogram and the time interval and symptoms, even though the two latter factors are considered in conjunction. However, for four of the ninety-five patients, repeat records showed a diminution in the degree of abnormality when compared with the records taken earlier in the course of the disease.

In this series of ninety-five cases of cerebrovascular disease, epileptic attacks occurred in fourteen. Of the five cases of jacksonian seizures, only one yielded a high degree of electroencephalographic abnormality of asymmetric, focal type. None of the records showed a pattern indicative of a convulsive disorder.

A comparison of the frequency of various types of electroencephalographic records in cases of cerebrovascular disease with the frequency of the same types of records in cases of hemispheric tumors demonstrates the fact that certain types of records (that is, asymmetric records and records with a focus) make the diagnosis of a brain tumor much more probable than that of a cerebrovascular lesion. It also shows that no one type of record is specific for one or the other type of cerebral lesion.

BELLET.

Jones, N. W., and Rogers, A. L.: Chronic Infection and Atherosclerosis. Arch. Path. 45:271 (March), 1948.

The authors report additional data to support their belief that cardiac failure, secondary to coronary atherosclerosis, will respond favorably, in certain cases, to the removal of focal infection. Their interest is centered particularly in chronic hyperplastic disease of the paranasal sinuses, in which lesion they emphasize the common occurrence of arteriolar sclerosis, of thrombosis of small arteries, and the presence in tissues of microorganisms, chiefly diplococci, presumably streptococci. The authors believe that nasal infection may reach the systemic circulation by means of the lymphatic connections between the paranasal sinuses and the paratracheal lymphatics, thence by the great veins to the right heart, a route of infection often mentioned by the otolaryngologists.

The authors are impressed by local arterial and arteriolar thickening in response to local infection. Their work does not reveal whether such changes necessarily reflect the presence of a widespread systemic atheromatosis. Their experimental work consisted of the injection of cultures of streptococci into the paralaryngeal lymph nodes of cats. The organisms were obtained from the hyperplastic antral mucosa of a patient with coronary artery disease. While such organisms were recovered on culture of the cat's aorta and coronary artery tissue, also of liver and spleen, no atheromatous coronary lesions were found in similarly treated animals allowed to live for many months.

However, the authors found some evidence for the validity of infectious lymphatic transportation from the neck to the chest. After injecting trypan blue into the paralaryngeal lymph nodes of cats, they found large phagocytes laden with the blue pigment in the walls of the ascending arch of the aorta.

GOULEY.

Steiner, A.: Effect of Choline in the Prevention of Experimental Aortic Atherosclerosis. Arch. Path. 45:327 (March), 1948.

The lipotropic action of choline on the fatty infiltration of the liver in depancreatized dogs led Steiner to add this substance to the cholesterol diet fed to rabbits for the production of hypercholesterolemia.

Fifty-four rabbits, divided into two approximately equal groups, one a control receiving cholesterol without the supplementary choline, were killed at periods varying from 40 to 100 days. They were autopsied with special attention being paid to the degree of aortic atheromatosis in the two contrasting groups. While the ingestion of choline did not affect the level of hypercholesterolemia, it retarded and reduced the development of atheroma in the aorta of the rabbit. Steiner found a definite quantitative relationship between the amount of choline ingested and the degree of protection against atheromatosis.

The action of choline in this respect remains unknown, differing from that of thyroid extract and of iodine, which prevent the inception of hypercholesterolemia.

GOULEY.

Wyatt, J. P., and Goldenberg, H.: Amniotic Fluid Embolism. Arch. Path. 45:366 (March), 1948.

The authors report a case of sudden death due to pulmonary embolism occurring in the first stage of delivery. The patient lived only fifteen minutes from the time of acute onset. Following the rupture of the membranes she became acutely dyspneic and cyanotic. Histologic examination revealed the cause, namely, amniotic fluid embolism originating most probably in the abrasion of the endometrial surface of the lower uterine segment with subsequent tearing of uterine veins and sinusoids. Microscopic examination revealed not only uterine epithelial fragments, but also mucin within pulmonary arterioles.

The diagnosis was made only by microscopic study, since this type of embolism involves small pulmonary vessels. The authors believe with Steiner and Lushbaugh, who originally reported this obstetrical catastrophe, that its incidence is undoubtedly greater than is generally known, and that it is obscured under diagnoses of acute pulmonary edema and obstetrical shock.

GOULEY.

Leicher, F.: Pathogenesis of Primary Epithelial Tumors in Human Conduction System. Ztschr. f. Kreislaufforsch. 37:8 (March), 1948.

To the five instances of primary tumors of the conduction system encountered in literature two new observations are added. One concerned a woman who died at the age of 24 years after having shown A-V block for two years; the other tumor was found in the heart of a woman 34 years old who had been known to have cardiac disease since her youth. Typical Adams-Stokes seizures were present in both patients.

In the region of the A-V node in both instances there was a small tumor of an identical structure: a mixture of collagenous and connective tissue cells of varying character and cysts lined by cells of epitheloid appearance. However, atypical or polymorphic cells or mitoses were not encountered. The microscopic findings are analyzed and compared with previously described cases of tumors in the conduction system. It is concluded that these tumors are hamartomas growing from epithelial tissue, the origin of which is to be sought in elements of the caudal portion of the primitive intestine which had been displaced into the atrial septum.

BRUMLIK.

Moll, A., and Korth, C.: Electrocardiographic Diagnosis of Left Ventricular Hypertrophy. Ztschr. f. Kreislaufforsch. 37:125 (March), 1948.

The well-known electrocardiographic combination of left axis deviation, depression of S-T_1, inverted T_1, and positive T_3 is classified as "the hypertrophy form." However, it is not simple hypertrophy and dilatation of the left ventricle which is at fault: the electrocardiographic change is due to a hypertrophied and dilated left ventricle which is also in failure because of myocardial damage.

The same pattern is found after the administration of digitalis following infarction of the anterior surface of the heart, during the course of general infections, following thyroidectomy and tonsillectomy, and when left ventricular activation is delayed. In these instances the pattern is transient; if the hypertrophy of the left ventricle, etc., is the underlying cause, the pattern is permanent.

Great emphasis is laid on a subtle distinction between the convex "hypertrophy S-T form" ("Hypertrophieform des Mittelstücks") and the sagging ("muldenförmig") depression of this segment which is considered to be a typical expression of coronary insufficiency, digitalis effect, and toxic damage of the myocardium (for example, diphtheria). In the opinion of the authors the "Hypertrophy ECG" implies a very serious prognosis.

BRUMLIK.

Krick, J.: *Transverse and Longitudinal Extensibility of Arteries.* Ztschr. f. Kreislaufforsch. 37:140 (March), 1948.

This paper summarizes the results obtained in experiments on surviving and devitalized (desiccated or boiled) beef arteries. There is a considerable difference between the extensibility of the aorta and its branches: in the aorta the transverse extensibility is predominant, whereas the large arteries (carotid more than the femoral) rather show an increase in longitudinal extensibility. Veins possess a more pronounced transverse extensibility than arteries. After killing by desiccation and resoftening, the extensibility of the aorta and the arteries changes little; in contrast, boiling diminishes the longitudinal extensibility of the arteries considerably, but that of the aorta is diminished relatively little.

It is concluded that the extensibility of the arteries, which is a function of the histomechanical arrangement of their wall tissue, is not destroyed by dehydration but that it is diminished by heat.

BRUMLIK.

Crosby, R. C., and Wadsworth, R. C.: Temporal Arteritis. Arch. Int. Med. 81:431 (April), 1948.

The essential features of forty-three previously reported cases of temporal arteritis, as well as five additional cases reported in this paper, are presented and analyzed. The pathologic

changes in biopsy specimens of artery segments in one case are described in detail and consist of a granulomatous type of reaction involving all coats of the artery but usually greatest in the media. Areas of necrosis are accompanied by a diffuse infiltration of cells in which the mononuclear varieties seem to predominate. Multinuclear giant cells are conspicuous but there is little to suggest any relationship to tuberculous, syphilitic, or rheumatic arteritis. The internal elastic lamina seems to act as an imperfect buffer against internal progression of the process to the intima; but with progression of the inflammatory process into the intima there may be destruction of the endothelial lining and the development of thrombi with obliteration of the lumen. This process can also extend through the periadvential tissue where it will surround but not penetrate the periarterial nerves. Compressions of these nerves may contribute to the pain of which these patients complain. A dissecting aneurysm of one temporal artery and phlebitis of the accompanying veins was also found. Blindness is a common complication occurring in one or both eyes of 33.3 per cent of the cases and the possible prophylactic value of section of the middle temporal artery early in the disease is suggested.

The authors conclude that temporal arteritis is a distinct clinical entity, affecting people of the older age group, which has a mortality (12.5 per cent) which is considerably less than that of most other forms of arteritis and for which the cause is unknown. The systemic symptoms probably indicate a more generalized arteritis, but since the temporal vessel involvement and symptomatology arising from it are constant and dominant features of the disease, it is suggested that the term "temporal arteritis" be retained until etiological classification is possible.

BERNSTEIN.

Zelman, S., and Gilbert, T.: Cytochrome C Therapy of Tissue Anoxia in a Case of Hepatolenticular Degeneration. Arch. Int. Med. 81:485 (April), 1948.

A case of hepatolenticular degeneration (Wilson's disease) is described in which the bright venous blood and the presence of clubbing of the fingers seemed to point toward the existence of a relative anoxia. The authors, therefore, after a very complete chemical-clinical work-up prepared cytochrome C from equine hearts and administered it to their patient along with sodium succinate (shown to participate in another pathway of oxidative metabolism leading up to the cytochrome series and a known potentiator when used with cytochrome C).

The patient, a 30-year-old white veteran, seemed to require unusually large amounts of cytochrome C since the desired end point of a pink color in the plasma was obtained only intermittently with 80 mg. or more daily, intramuscularly. This pink color was believed to represent a spill-over into the serum of any unneeded excess but has been shown to be really due to the presence of hemoglobin as a result of slight hemolysis. The patient seemed to improve clinically within a few days, but the authors caution against undue enthusiasm since the intensity of symptoms of parkinsonism is commonly observed to vary with the patient's mood and remissions have been described in Wilson's disease.

After two months of continuous therapy he was able to speak, feed himself, and walk unassisted. Edema of the legs disappeared (first time in three years) and clubbing diminished. The metabolic rate returned to normal, indicating an increased consumption of oxygen. Venous blood, formerly red to purplish, now varied from blue to a deep blue-black. Arteriovenous oxygen differences, formerly below normal, were considerably increased. These facts alone indicate a definite increased utilization of oxygen by the tissues. Fatal relapse occurred when administration of cytochrome C was discontinued because of the development of eosinophilia; terminal reinstitution of cytochrome therapy proved ineffective. Autopsy revealed pathologic changes referable to anoxia, but less marked than expected. This, as well as a remarkable degree of hepatic regeneration, may have been influenced by the therapy with cytochrome C.

BERNSTEIN.

Master, A. M.: Apical Systolic Murmur. Arch. Int. Med. 81:518 (April), 1948.

The author believes, and quotes numerous extensive personal and insurance statistics to support his belief, that loud apical systolic murmurs, even in the absence of cardiac enlarge-

ment, heart failure, diastolic murmurs, or abnormal electrocardiograms, are a sign of organic heart disease. The over-all mortality for persons under 40 years of age with apical systolic murmurs is 3.25 times higher than the normally expected mortality rate and 4.5 times higher when there has been a history of rheumatic fever. The mortality rate is 50 per cent higher among manual workers with apical systolic murmur than among "white collar workers."

It should be evident then that the proper evaluation of the murmur is of paramount importance in medical practice both in war and in peace. Use of the term "loud apical systolic murmur" includes all grades of intensity except the extremely faint and slight and will include the moderately loud, loud, extremely loud, and unusually loud murmur (classification of Freeman and Levine). Physical examination, history, and laboratory examination are still of major importance in the final determination. A history of rheumatic fever in a patient with a loud murmur should be accepted as almost certain evidence that a defect in the mitral valve exists. The presence of a "musical, harsh, sea-gull, or constant murmur" strengthens the diagnosis. Patients should be examined repeatedly, in different positions and after exercise, since the murmurs of early valvular heart disease are transient.

Exercise will not produce "loud" apical murmurs in healthy persons. The teleroentgenogram and fluoroscope are of considerable import in diagnosis, as is the electrocardiogram. The occasional difficult differential diagnosis from the "effort syndrome" can usually be made on the basis of other well-recognized symptoms of neurocirculatory asthenia.

The author believes that loud systolic murmurs at the apex should therefore be considered organic, and the patient treated accordingly, receiving antibiotics during various manipulations and diseases which injure the mucous membranes and facilitate the entrance of bacteria into the blood stream which may lead to bacterial endocarditis. Establishment of the organic nature of a murmur does not afford a criterion of the heart's function.

BERNSTEIN.

Tannenbaum, I., and Ferguson, J. A.: Rapid Deceleration and Rupture of the Aorta. Arch. Path. 45:503 (April), 1948.

This report deals with the possible importance of rapid deceleration as a factor in rupture of the aorta, a problem heretofore chiefly of interest in aviation medicine.

The authors record the presence of clean rupture of normal aortas following automobile accidents. In both instances the vehicle hit an immovable obstacle head-on. The drivers developed shock and died within a few minutes. Autopsy revealed aortic rupture at a classical site, namely, the junction of the descending aortic arch with the thoracic aorta.

The authors stress what they term "minimal damage to the thoracic cage," which is often in striking contrast to the rupture of a normal aorta.

GOULEY.

Penneys, R., and Thomas, C. B.: Oximeter Control of Arterial Oxygen Saturation in Anoxemia Studies. Bull. Johns Hopkins Hosp. 82:470 (April), 1948.

The purpose of this study is to describe a procedure capable of producing the same constant level of anoxemia, which would remove an important obstacle in the standardization and further use of the "anoxemia test" of cardiac function. Its principle is based on the fact that by continuous fine adjustment of the oxygen concentration in a gas mixture, a constant degree of anoxemia, as measured by the oximeter, may be induced in the same and different individuals. This preliminary report is concerned with observations on normal subjects at levels of 85 per cent, 80 per cent, and 75 per cent arterial oxygen saturation. The lower level was set at 75 per cent for the following reasons: it is the approximate average arterial oxygen saturation resulting from 10 per cent oxygen inhalation; there is considerable cardiovascular stress at this point; and it provides a safe margin before marked central nervous system symptoms appear. The ability to produce and maintain any level of arterial oxygen saturation accurately depends more on the subject's being at ease than on any other factor.

The electrocardiograms were studied for any abnormalities, especially changes in the RS-T segments and T waves. In each of the four subjects studied at the three levels of anoxemia, 85 per cent, 80 per cent, and 75 per cent, no striking differences were observed between the various levels. Also, there were no marked differences noted between the electrocardiograms taken after ten and twenty minutes of anoxemia.

The oximeter was found to give the same degree of stability at the different levels. It can be said, therefore, that vasomotor changes due to anoxemia, and their effect on the thickness of the ear, do not alter the stability of the oximeter in the range of 75 to 100 per cent arterial saturation.

None of the subjects had symptoms at 85 per cent or 80 per cent arterial saturation. No changes in blood pressure, pulse, or respiration, necessitating termination of a test period, were encountered at these levels.

It is believed that this method is considerably more accurate than the currently used "induced anoxemia test" in which the subject inhales a gas with a fixed oxygen concentration (10 per cent).

BELLET.

Lowe, T. E., and Bate, E. W.: The Diameter of Cardiac Muscle Fibres: A Study of the Diameter of Muscle Fibres in the Left Ventricle in Normal Hearts and in the Left Ventricular Enlargement of Simple Hypertension. M. J. Australia 1:467 (April 10), 1948.

In this investigation the authors determined the transverse diameters of cardiac muscle fibers in each of the four major layers of the left ventricular wall in normal hearts and in hearts hypertrophied from simple hypertension. The hearts used in this investigation were five macroscopically normal ones from young adults and two from adults who had simple hypertension without congestive cardiac failure and who died noncardiac deaths. All hearts after fixation appeared to be in a comparable phase of partial systole.

In the normal hearts there was only a small variation in fiber size and the distribution of fibers of various sizes was symmetrical about the mean. There was also marked uniformity between the three outer layers, but the mean value for the inner layer was significantly smaller than that for the other layers. In the hypertrophied hearts there was enlargement of fibers and increase in the range of fiber size; the distribution of fiber size about the mean was symmetrical. In contrast to the finding in the normal hearts, the mean fiber size in the internal layer in this group was not significantly different from that in other layers.

Several methods of approach already considered suggest that there is a "limit of hypertrophy" of cardiac muscle fibers. This concept gives a ready explanation of the observation that the mean fiber size and distribution of fiber size in the two hypertrophied hearts examined were almost identical, despite the marked difference in weights. The marked difference in the weights of the hypertrophied hearts with the same fiber diameters shows that, in itself, heart weight is not necessarily a good index of the degree of muscle hypertrophy. The differences in weight must therefore be due to alterations in the amounts of interstitial fluid or tissue.

If the tension which a muscle fiber can develop is proportional to its cross-sectional area (Harrison), in each of the hearts examined a striking uniformity of tension in the muscle layers of the left ventricle can be deduced. In the hypertrophied hearts the mean cross-sectional area of fibers in each layer was the same. In the normal hearts, however, the mean cross-sectional areas of fibers, while uniform in the outer layers, were slightly but significantly less in the innermost layer. These observations imply, therefore, that in the normal heart the tensions are uniform in the outer three layers and slightly less in the innermost layers. In the hypertrophied hearts the tension seems to be uniform in all layers.

BELLET.

American Heart Association, Inc.

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AMERICAN HEART ASSOCIATION AWARDS $250,000 FOR RESEARCH

The Board of Directors of the American Heart Association, on March 8, 1949, approved the report of the Research Committee and the Executive Committee of the Scientific Council allocating approximately $250,000 for fellowships for established investigators, research fellowships, and grants-in-aid.

The awards were made in accord with approved policies recommended by the Research Committee of the Scientific Council.

Research Policies

The following policies, formulated by the Research Committee at its meeting in Chicago on February 26, 1949, were adopted as a guide in awarding research grants:

1. The funds allocated to individuals at present shall be given in major degree to Research Fellows as compared to Established Investigators.

2. Career Investigators shall not be appointed at the present time.

3. (a) Grants-in-Aid shall not be approved at the present time except in unusual circumstances.

(b) Fifteen per cent of the total research funds ($37,500) shall be granted for cooperative research studies (for example, The Evaluation of Anticoagulants in the Treatment of Coronary Thrombosis With Myocardial Infarction).

4. Fluid Grants shall not be approved at the present time.

5. A decision concerning the division of funds for any particular cardiovascular disease or function is not warranted at the present time.

6. Ten per cent of the present funds allocated for research ($25,000) shall be given for basic research. Cooperation in this endeavor shall be sought with other large national voluntary organizations with the hope that a general Panel Committee of all of these may be formed to administer the funds contributed by them for basic research.

7. Funds shall not be approved for general teaching, nor for isolated statistical studies in clinical investigation.

8. Funds approved for Grants-in-Aid, or to individuals for Fellowships, shall be set aside for the current year only. Approval of a Grant-in-Aid or an Established Investigator shall include a statement of the duration of future support and a statement that such support will be contingent upon the availability of funds.

Applications for Fellowships shall be reviewed in October preceding the academic year in which the fellowship is desired, and research Grants-in-Aid for the individuals supported by these fellowships or other independent applications for Grants-in-Aid shall be considered in February preceding the academic year in which they are to start.

9. A separate contingency fund for research is not approved. However, the general reserve funds of the American Heart Association, after proper recommendation by the Research Committee, may be made available for the support of research in those unforeseeable circumstances which would call for immediate action.

10. It is anticipated that cooperative research will be participated in and supported by local heart associations and the American Heart Association will supplement these funds up to fifteen per cent of its present research funds.

Awards

The following research awards were allocated for the period of one year to begin in most instances on July 1, 1949.* Indicated are the institutions or places where the research will be conducted.

I. *Established Investigators*

Awards totalling $12,500 were made to J. R. Elkinton, M.D. (University of Pennsylvania); W. Mommaerts, Ph.D. (Duke University).

II. *Research Fellowships*

Awards ranging from $3,000 to $4,000 each, and totalling $103,600, were allocated to the following: G. R. Denton (Albany Medical College); G. C. Sutton (Sweden); C. G. Sawyer (Peter Bent Brigham); T. G. Schnabel (University of Pennsylvania); P. Scheinberg (Duke University); E. Watkins, Jr. (University of Oregon); J. H. Heller (Yale University); R. J. Jones (University of Chicago); L. C. Mark (New York University); A. Genecin (Johns Hopkins University); E. Lepeschkin (University of Vermont); A. A. Brust (Cincinnati General Hospital); W. B. Schwartz (Harvard University); A. Mascatello (Long Island College of Medicine); L. S. Sommer (Columbia University); A. P. Fishman (Mt. Sinai Hospital, N. Y.); E. L. Foltz (University of Pennsylvania); W. W. Hurst (Deaconess Hospital, Great Falls, Mont.); C. A. Stetson (Rockefeller Institute, N. Y.); R. W. Oblath (May Institute, Los Angeles); F. J. Kelly (Tulane University); S. Kobernick (McGill University); L. Tobian, Jr. (Southwestern University); F. H. Taylor (Duke University); J. P. Merrill (Peter Bent Brigham); E. H. Kass (Good Samaritan Hospital, Boston, Mass.); J. E. Warren (Good Samaritan Hospital, Boston, Mass.); R. E. Olson (Harvard University); A. G. White (Montefiore Hospital, N. Y.).

III. *Research Grants-In-Aid*

Research grants totalling $23,730 were made to the following investigators: R. F. Loeb (Columbia University); R. M. Reinecke (University of Minnesota); C. H. Thienes (University of Southern California); D. A. Rytand (Stanford University); O. W. Sartorius (Syracuse University); R. E. Gross (Children's Hospital, Boston).

Grants of $11,235 to the following were approved and will be allocated if funds are available: Mary Colglazier (University of Kansas); E. Watkins, Jr. (University of Oregon); J. R. DiPalma (Long Island College of Medicine); J. J. Sampson (Mt. Zion Hospital, San Francisco).

Grant-In-Aid for Training Program

Allocation of $16,170 was approved for the establishment of a special training program for cardiovascular investigators under Dr. Carl J. Wiggers at Western Reserve University. The program will be supported on a cooperative basis with the National Heart Institute. Under this plan, a maximum of ten investigators selected by Dr. Wiggers will receive training in various research methods employed in human and in animal cardiovascular research for a period of one year. The National Heart Institute will support the individuals chosen for this program, and the American Heart Association is supporting the cost of the training program.

*$25,000 was awarded to Dr. Albert St. Gyorgyi for research on muscular contraction by the Board of Directors last June.

Research Fellow of the Cardiovascular Registry

A resolution was approved by the Board of Directors providing for the establishment of a Research Fellowship for the Cardiovascular Registry of the American Registry of Pathology from the funds allocated for cooperative research studies. The funds will be administered by the Advisory Committee on Cardiovascular Registry.

Further information about these grants and present policies of the Research Committee may be obtained by writing to Dr. Charles A. R. Connor, Medical Director, American Heart Association.

ANNOUNCEMENT

A symposium on Water and Electrolyte Metabolism in Cardiac Edema, sponsored by the Cardiovascular Study Section of the National Institutes of Health of the Public Health Service, will be held on April 30, 1949, at Hotel Haddon Hall, Atlantic City. Dr. E. Cowles Andrus, Baltimore, is Chairman of the Cardiovascular Study Section.

It will be appreciated if those who expect to attend will communicate with Dr. Eleanor M. K. Darby, National Institutes of Health, Bethesda, Maryland, Executive Secretary.

THE AMERICAN SOCIETY FOR THE STUDY OF ARTERIOSCLEROSIS

The American Society for the Study of Arteriosclerosis will meet in Chicago, November 6-7, 1949. Titles submitted for the program must be in the hands of the Chairman of the Program Committee, E. Cowles Andrus, M.D., 24 East Eager Street, Baltimore 2, Md., by June 15. Titles should be accompanied by an abstract of not more than 300 words.

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Original Communications

OBSERVATIONS ON THE ANATOMY OF THE ATRIOVENTRICULAR BUNDLE (BUNDLE OF HIS) AND THE QUESTION OF OTHER MUSCULAR ATRIOVENTRICULAR CONNECTIONS IN NORMAL HUMAN HEARTS

Albert D. Kistin, M.D.
Washington, D. C.

According to the present most widely accepted view, the impulse to contraction in the human heart is conducted from the atria to the ventricles by way of a single muscular atrioventricular bundle (bundle of His) located at the cephalic end of the interventricular septum. The bundle originates in a distinct atrioventricular node (node of Tawara) lying on the right side of the interatrial septum a short distance ventral to the coronary sinus. The atrioventricular node has a number of connections with myocardial fibers of the right atrium. The cardiac impulse is believed to originate in the sinoatrial node located at the junction of the superior vena cava and the right auricle. The atrioventricular bundle divides into two branches, right and left, which descend on the respective sides of the interventricular septum. The anatomic basis for this concept has been established through the studies of a number of investigators.[1-26] By analogy with what has been observed in sheep and bovine hearts, it is believed that each bundle branch forms a widespread subendocardial network in man, but this has not been demonstrated. In sheep and bovine hearts a tough sheath surrounds the atrioventricular bundle, and dye injected within the sheath passes out to the finest branches of the terminal network in the ventricles outlining a complex atrioventricular fiber system.[27-33] In the human heart, however, there is no sheath about the atrioventricular bundle and heretofore, attempts at demonstration by dye injection have failed.

Glomset and Glomset[34,35] and Glomset and Birge[36] have questioned the entire concept of the muscular atrioventricular conduction system. Among the conclusions of these authors concerning the human heart are the following:

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From the Cardiovascular Research Unit, Veterans Administration, Washington, D. C.

(1) the bundle of His is inconstant; (2) there are no muscular connections between the bundle of His and the right atrium; (3) the bundle of His does not bifurcate and, therefore, has no left branch; (4) there is no distinct node of Tawara; and (5) there are many atrioventricular connections in various regions of the heart. These authors find no anatomic basis for the myogenic theory of cardiac conduction. They find a well-developed intrinsic nervous system in the heart which they believe must be taken into account for an understanding of cardiac conduction.

These conclusions require serious consideration. If they are correct, it becomes necessary to revise accepted physiologic concepts including much of the theoretical basis of electrocardiography and the interpretation of abnormal rhythms and heart block. In the present study these conclusions were not confirmed, but instead the observations are in accord with the more generally accepted view of the anatomy of the human atrioventricular node and the atrioventricular bundle and its branches.

THE "PURKINJE FIBERS" AND METHODS OF STUDY

In 1845, Purkinje[37] described distinctive fibers in the hearts of sheep and other animals. Compared with ordinary myocardium, these fibers are considerably larger, their myofibrils are much sparser, and the cross striations are less distinct. The nuclei lie within a prominent clear region of sarcoplasm and the myofibrils tend to be arranged near the periphery. Tawara's great contribution[4] was the demonstration that the bundle described by His and the fibers described by Purkinje were parts of a single atrioventricular system. He showed that the bundle of His divided into two branches, each of which could be followed a relatively long distance down the septum and which expanded into complex fiber networks, the components of which were histologically identical in some animals with the fibers described by Purkinje. It is important to point out that Tawara recognized substantial histologic differences between the component fibers of the atrioventricular systems of different animals. He found that the microscopic characteristics of the fibers of man and dog were quite different from those of sheep; that they were much less distinctive and more nearly resembled ordinary myocardium.

Against this historical background it may be easier to evaluate two different methods that have been used to look for an anatomic basis for a myogenic conduction system in man and to appreciate two different implications of the term, "Purkinje fiber." Some investigators have searched sections of various parts of the human heart for fibers with the microscopic characteristics of the fibers first seen by Purkinje in sheep.[38,39] It is sometimes assumed that human conducting fibers must have this microscopic structure, and that all fibers with this structure are necessarily conduction fibers. From this point of view, the criterion for a "Purkinje fiber" is its microscopic appearance.

A different method of study has been to identify the muscular atrioventricular bridge in serial sections. Investigators who used this method[4,8,10,21,23] agreed that in man there is an atrioventricular node and an atrioventricular bundle and

branches in exactly the same anatomic location and with the same anatomic relationships as in other animals. They observed, on the other hand, that the histologic structure of the components of this atrioventricular fiber system in man is generally quite different from that of the sheep. From this second point of view the term "Purkinje fiber" often refers to the fiber components of the muscular atrioventricular conduction system without any commitment regarding special microscopic structure. Investigators using this method of study accept the proposition that homologous structures may become histologically different in different animals and still serve similar functions.

A recent study of the human moderator band[39] illustrates very well the difference between the two points of view. Since the course of the right bundle branch has previously been described along the moderator band, the authors sought here "Purkinje fibers" by microscopic criteria. They describe such fibers and state that there are numerous connections between them and adjacent myocardium. However, other investigators who have traced the human right branch in serial sections from the atrioventricular bundle state that its microscopic structure is indistinguishable from that of adjacent myocardium, and that it can be traced all the way to the base of the anterior papillary muscle of the right ventricle as a distinct muscle bundle without giving off any branches to adjacent myocardium.[21,22] Obviously the two groups of investigators are not describing the same thing.

In the present study the method of serial sections was employed, for it seemed to be the most reliable method. In considering theories of conduction of the cardiac impulse the important question is whether a muscular bridge exists between atria and ventricles, without any prior assumptions concerning special structural characteristics of such a bridge.

MATERIAL AND METHODS

Microscopic Studies.—The hearts of three adults and one newborn infant were studied. Except for slight to moderate coronary arteriosclerosis in the adult hearts, all four were anatomically normal. The electrocardiograms of two of the adults recorded shortly before death showed no conduction disturbances or other abnormalities. In the other two cases electrocardiograms were not obtained.

Blocks were cut and numbered in sequence around the atrioventricular orifice. Each block consisted of the entire thickness of atrium (or interatrial septum) and ventricle (or interventricular septum) and included a portion of atrium above the fibrous atrioventricular ring and a portion of ventricle below the ring (except the blocks including the part of the mitral valve attached to the aorta, which, of course, contained no ventricular portion below). A small portion of valve was left attached to the atrioventricular junction. The plane of cutting was approximately in a radius of the atrioventricular orifice and perpendicular to the atrioventricular ring. The sections were 10 microns thick and were stained by Masson's method,[40] which differentiates connective tissue (stained blue) from muscle (stained pink to red).

From two of the adult hearts serial sections were prepared from blocks completely encircling both atrioventricular orifices. These included sections from the regions of the interatrial septum and the upper part of the interventricular septum where the atrioventricular node, the bundle of His, and the origins of the bundle branches have been observed. The location of these structures is fully discussed and illustrated in the text to follow. From the third adult heart serial sections were prepared from blocks completely encircling the mitral orifice, and, in addition, serial sections were prepared for location of the atrioventricular node, the bundle of His, and the origins of the bundle branches. Every tenth section of the series was mounted and studied. By every tenth section being mounted, the usual gap between studied sections was 0.09 millimeter. Some of the sections mounted were unsuitable for study, producing a number of larger gaps in the series. A single poor section between two good ones enlarged the gap to 0.19 mm.; two consecutive poor sections, to 0.29 mm.; and three consecutive poor sections, to 0.39 millimeter. There were a number of gaps 0.19 mm. thick in all three adult hearts. There was one gap 0.29 mm. thick in the heart in which the mitral ring was studied. In one of the hearts in which both rings were studied there were two gaps of 0.29 mm. and two others of 0.39 millimeter.

From the heart of the newborn infant a series of sections was prepared for the study of the atrioventricular node, the atrioventricular bundle, and the origins of the bundle branches. In this series every section was mounted and studied. There were no gaps thicker than 30 microns. In addition, series in which each section was mounted and studied were prepared from a number of regions about both atrioventricular orifices, although these did not constitute complete series about either orifice.

Macroscopic Studies.—Dissections of more than forty human hearts were carried out under a binocular dissecting microscope. A magnification of seven times was found to be very satisfactory; it provided adequate magnification and at the same time was not so great as to obscure relationships. Most of the hearts were examined after fixation in formalin, but a number also were examined unfixed soon after removal at autopsy.

SERIAL SECTIONS OF THE ATRIOVENTRICULAR NODE (NODE OF TAWARA), THE ATRIOVENTRICULAR BUNDLE (BUNDLE OF HIS), AND THE ORIGINS OF THE BUNDLE BRANCHES

The atrioventricular node appears as a distinct structure in microscopic sections (Figs. 1 and 3,*A*). It is a compact mass of interlacing, fine muscle fibers, the shape of an ovoid in cross section. It is found a short distance ventral to the coronary sinus and just above the attachment of the medial cusp of the tricuspid valve. One side of the node is separated from the endocardium of the right atrium by a thin layer of subendocardial atrial muscle and a variable amount of fat. The opposite side lies against the central fibrous body. The smallest dimension is between these two sides. The approximate maximum dimensions of the node in the three adult hearts are: dorsoventral, 3.6, 4.2, and 4.1 mm.; cephalocaudal, 4.0, 4.5, and 3.0 mm.; and thickness, 0.5, 1.0, and 0.75 millimeter.

The individual fibers of the atrioventricular node are thinner than the adjacent atrial fibers and stain slightly paler. The dense tangle of thin muscle fibers that constitutes the node is quite well demarcated from the surrounding looser arrangement of coarser atrial fibers. There are, however, in each case a number of connections of the atrial fibers with the fibers of the node (Figs. 1 and 3,*A*). In one of the hearts these are mostly in the cephalic and dorsal parts of the node. In the other hearts in addition to connections in these locations there are also a number of connections on the side of the node beneath the endocardium and in the caudal part of the node. A large artery is seen in the nodes

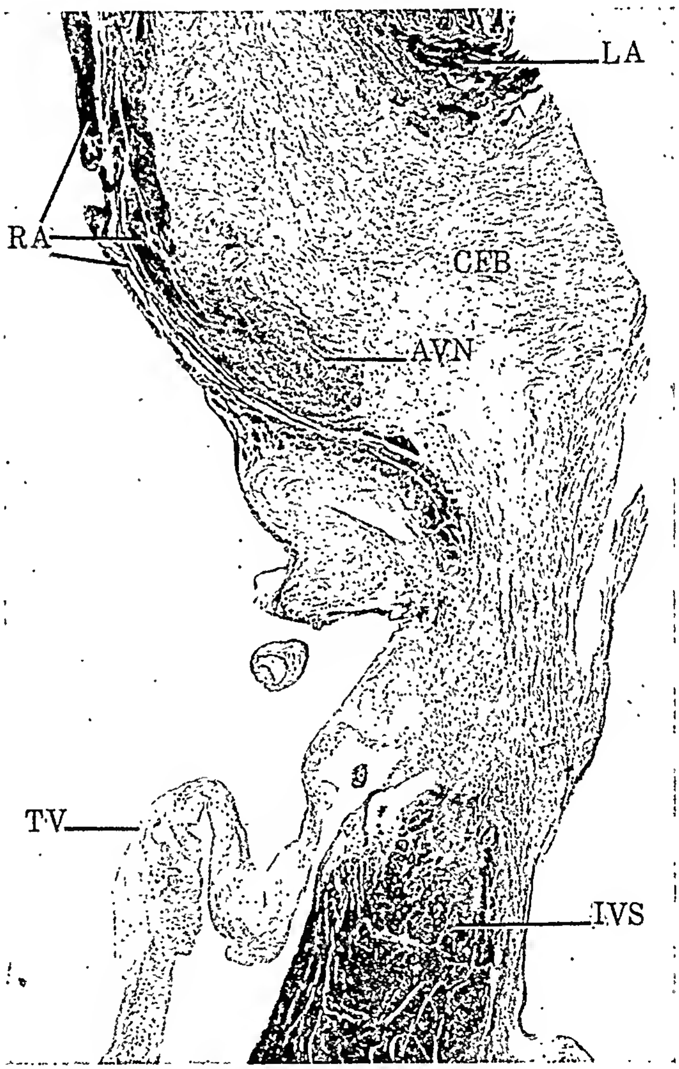

Fig. 1.—Photomicrograph of section from normal heart of newborn infant (× 17.8), Masson stain. *AVN*, atrioventricular node (node of Tawara); *CFB*, central fibrous body; *IVS*, myocardium of interventricular septum; *LA*, myocardium of left atrium; *RA*, myocardium of right atrium; *TV*, tricuspid valve. The connection of the node with the myocardial fibers of the right atrium is apparent. As in the other hearts studied, the structure designated here as atrioventricular node is seen to be continuous in serial sections with a distinct atrioventricular bundle which divides into two branches (see Fig. 3).

of the adult hearts and just to one side of the node of the heart of the newborn infant. In the node of the latter in addition to interlacing fibers there are regions of compact cellular masses.

The atrioventricular node is directly continuous ventrally with the bundle of His which can be traced section by section from the node through the central fibrous body and the membranous portion of the interventricular septum. The bundle lies in close association with the uppermost border of the muscular portion of the interventricular septum, although its exact relations vary somewhat in the different hearts (Fig. 2). In one adult heart the bundle, triangular in cross section, lies above the crest of the muscular portion of the interventricular septum throughout its extent (Fig. 2,*A*). In the other two adult hearts and in the heart of the newborn infant the dorsal portion of the bundle lies above the crest of the septum, but the ventral portion comes to lie on the left side of the septum (Fig. 2,*B*).

The shapes of the sections of the bundle vary in the different hearts and at different levels in the same heart. They are oval, roughly triangular, roughly quadrilateral, and entirely irregular. The intensity of staining of the bundle is slightly less than that of the adjacent myocardium. The individual fibers of the bundle are somewhat larger than those of the atrioventricular node but still smaller than the bulk of myocardial fibers forming the adjacent interventricular septum. There is a rapid transition from the interlacing network of the atrioventricular node to a more or less parallel arrangement of fibers in the bundle itself.

The division of the bundle is clear in all four hearts. The three-dimensional image obtained from tracing the serial sections is much more convincing than the few illustrations that can be shown (Fig. 3). The left branch is given off as a thin sheet of fibers seen on edge in the sections (Figs. 2 and 3), and the right branch seems to be a continuation of the bundle itself (Fig. 3). In three of the hearts the bifurcation is very close to the crest of the muscular portion of the interventricular septum, so that the branches descend immediately to the subendocardial regions of the respective sides of the septum. In one case, however, the bifurcation occurs on the left side of the septum some distance below the crest so that the right branch must penetrate a thickness of muscle in the upper part of the interventricular septum to reach its subendocardial position.

In the heart of the newborn infant a small strand is given off from the bundle a short distance after its origin from the atrioventricular node and before the division of the bundle into left and right branches. This strand descends into the muscular portion of interventricular septum and soon joins septal myocardial fibers. Similar connections have previously been described.[41,42] In the adult hearts small strands are given off from the atrioventricular bundle in a comparable location, but these seem to end in the central fibrous body without joining septal myocardium. It must be remembered that in the adult hearts only every tenth section of the series was studied, and the possibility of fusion of these small strands with septal myocardium in locations between the studied sections cannot be definitely excluded.

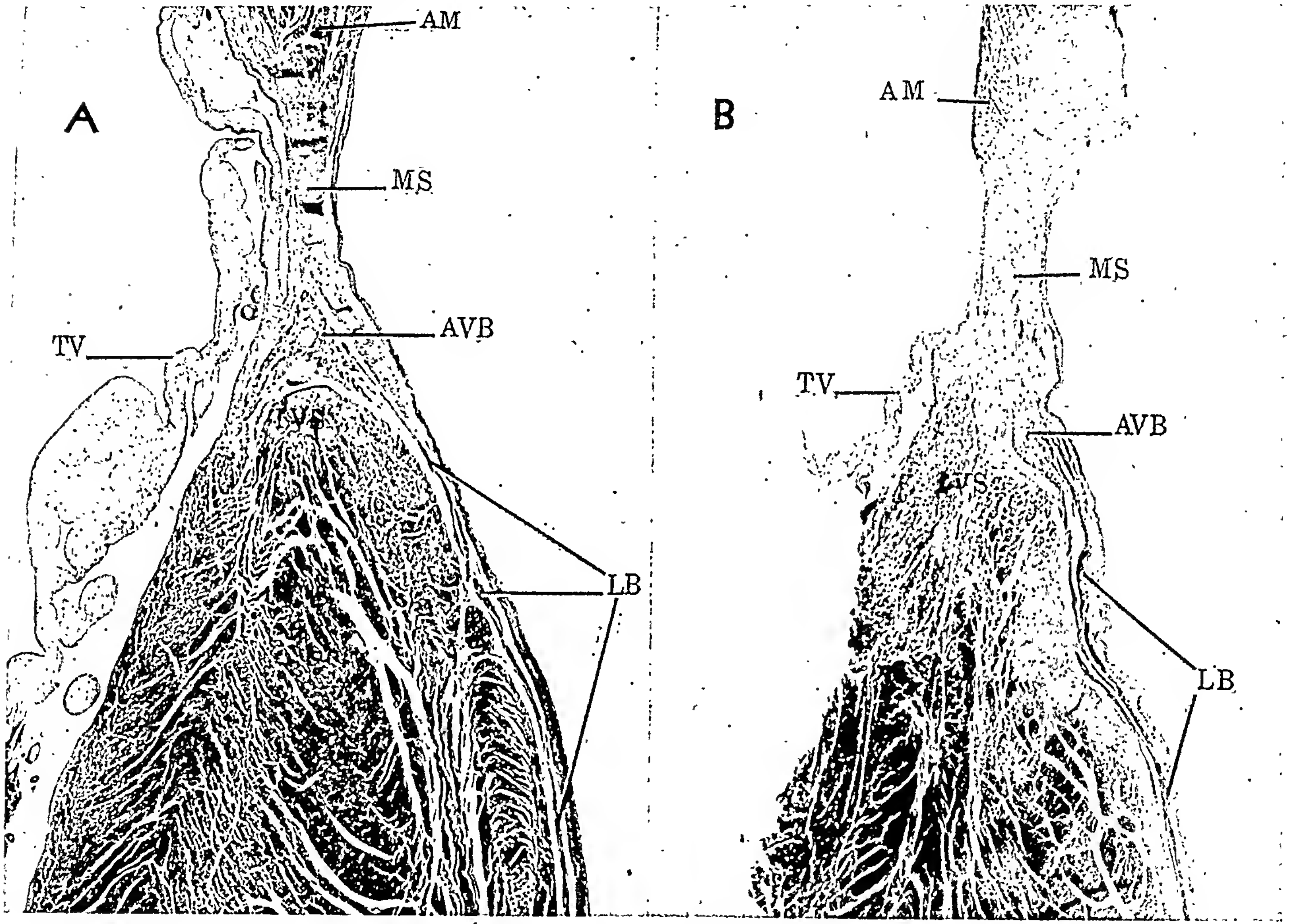

Fig. 2.—Photomicrographs of sections from two normal adult human hearts, showing the atrioventricular bundle (bundle of His) and its left branch (× 9.6). Masson stain. *AM*, atrial myocardium; *AVB*, atrioventricular bundle (bundle of His); *IVS*, myocardium of interventricular septum; *LB*, left branch of bundle; *MS*, membranous portion of interventricular septum; *TV*, tricuspid valve. The bundle shown in *A* lies within the membranous septum and could be readily exposed in dissection by an approach from either side of the septum. The bundle shown in *B*, however, lies below the membranous septum and is separated from the endocardium of the right side of the septum by a thickness of myocardium; exposure from the right side in this case would be more difficult than from the left.

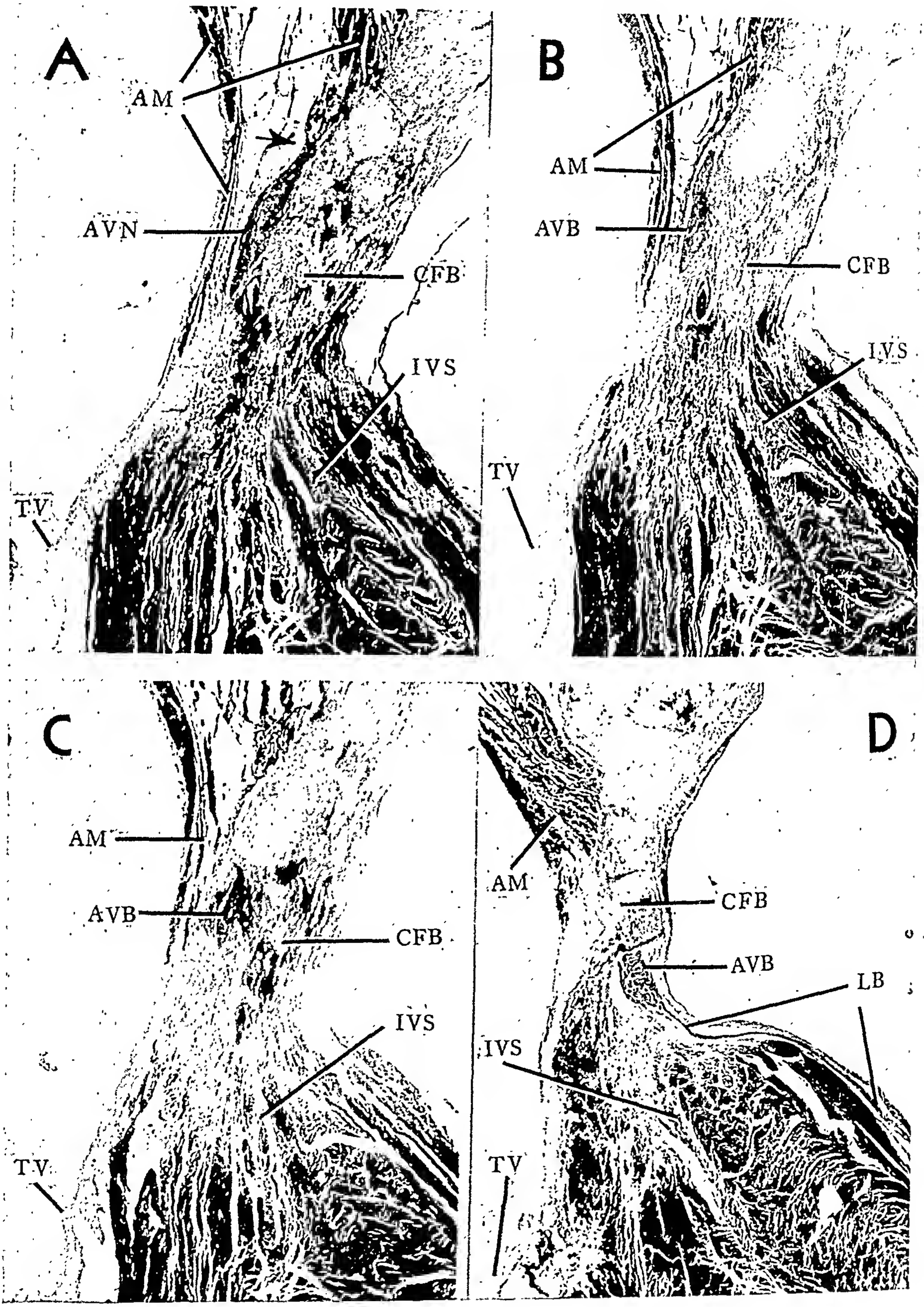

Fig. 3.- *A D. See opposite page for legend.*

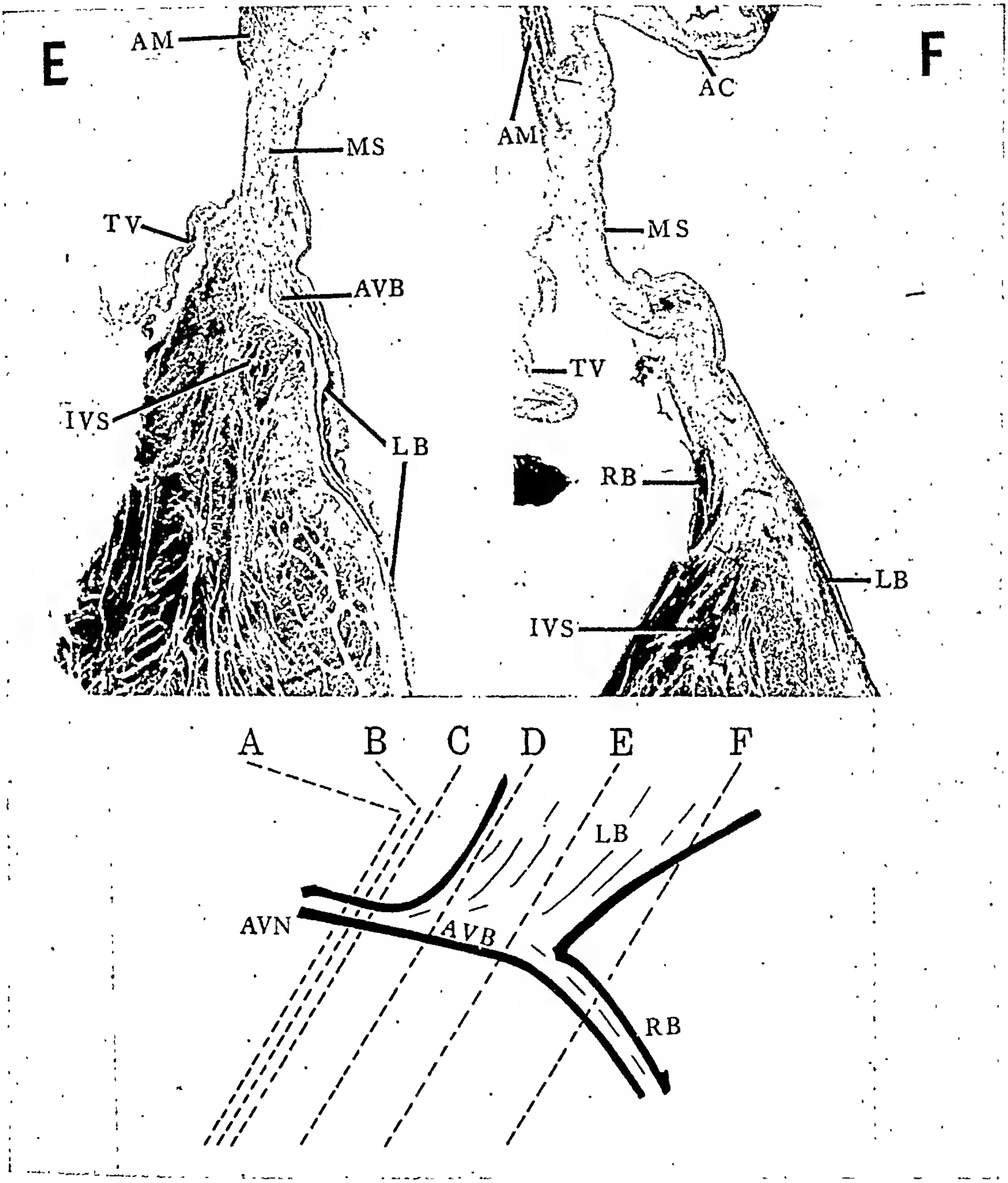

Fig. 3.—*A* to *F*, Photomicrographs of representative sections from a consecutive series from a normal adult human heart (× 8.3), Masson stain. *AC*, cusp of aortic valve; *AM*, atrial myocardium; *AVB*, atrioventricular bundle (bundle of His); *AVN*, atrioventricular node (node of Tawara); *CFB*, central fibrous body; *IVS*, myocardium of interventricular septum; *LB*, left branch of bundle; *MS*, membranous portion of interventricular septum; *RB*, right branch of bundlo; *TV*, tricuspid valve. There is direct continuity in the serial sections from atrioventricular node to atrioventricular bundle to bundle branches. The arrow in *A* points to connections of right atrial myocardium with the superior part of the atrioventricular node. The diagram shows the approximate levels of Sections *A* to *F* with reference to the atrioventricular node, the atrioventricular bundle, and the origins of the bundle branches seen from above. For orientation of the diagram in the heart, compare with Figs. 4 and 5. The distances of the sections from *A* are: *B*, 0.4 mm.; *C*, 0.8 mm.; *D*, 2.6 mm.; *E*, 5.1 mm.; and *F*, 8.6 millimeters.

The right branch can be traced section after section as a distinct muscle bundle. Soon after its origin from the bundle its fibers are indistinguishable on the basis of microscopic structure and staining characteristics from adjacent fibers of the interventricular septum.

The intensity of staining and thickness of the individual fibers of the left branch vary considerably. Near its origin from the bundle some of its fibers are more slender and stain paler than the other fibers of the myocardium and resemble the fibers of the atrioventricular bundle. Other fibers stain more deeply and are larger, resembling septal myocardial fibers. Still other fibers are larger than the adjacent septal fibers and contain large, clear, unstained regions within which the nucleus may be situated. The latter fibers fit to a large extent the description given for the "Purkinje fibers" of sheep, but this microscopic picture is not limited to fibers of the left branch for it is occasionally observed in other myocardial fibers which have no connection with the atrioventricular bundle or its branches so far as can be determined in serial sections. The variations in structure and staining within the left branch are sometimes observed along the length of a single muscle fiber. That is, a slender, paler-staining segment of a fiber may become continuous with a larger, more deeply staining segment; or a clear, unstained swelling appears in the course of a slender fiber. Sometimes a number of slender fibers fuse to form the large, clear segments.

It has been suggested that some of the cytologic features observed are due to artefacts.[24] In the present study this factor cannot be evaluated since the hearts were obtained in the usual manner at post-mortem examination, and there was a delay up to several hours between death and fixation of the organs.

MACROSCOPIC STUDIES

Some of the structures under discussion were demonstrated by naked-eye dissection by Retzer,[2] Keith and Flack,[5] Curran,[9] Robertson,[12] Holl,[13] Tandler,[14] Walmsley,[19] Yater, Osterberg, and Hefke,[20] and Walls.[26] De Gaetani[11] believed that the structures were inconstant. Holmes,[17] Mahaim,[21] and Evans[24] stated that naked-eye dissection was not possible. Yater,[20] in order to obtain relatively fresh specimens for microchemical analysis, found it possible to dissect the atrioventricular bundle within a few minutes in a large percentage of the hearts of adults. In the present study, by dissections carried out under a binocular microscope at a magnification of seven times, the bundle of His and the right branch were demonstrated in thirty-five of forty consecutive attempts. These forty dissections were carried out after preliminary studies to establish relationships and technique. In most of these dissections the origin of the left branch and the site of bifurcation were demonstrated as well.

The crucial landmark for dissection is the boundary between the membranous and muscular portions of the septum. A small segment of the medial cusp of the tricuspid valve must be removed to expose this region on the right side. On the left side this region is immediately below and between the posterior and right aortic cusps.

The Atrioventricular Bundle (*Bundle of His*).—The examination was usually begun on the right side. In some hearts the bundle may be seen without magnification and without dissection. It then appears as a whitish band in the lower part of the translucent membranous septum. In one heart it formed a round bulge in this region. Where the bundle is not immediately apparent the fibrous tissue at the boundary between membranous and muscular septa is carefully teased away. In most cases this exposes the bundle lying either entirely within the lower part of the membranous septum or partly in the membranous septum and partly on the muscular septum.

Under the discussion of the serial sections the variability of the exact location of the bundle was described (Fig. 2). In the dissections a better appreciation of this variability is obtained. In some cases the bundle lies on the left side just beneath the crest of the muscular septum, so that the approach from the right side may fail to expose it. The bundle illustrated in Fig. 2,*B* is an example. While the bundle lies superficially beneath the endocardium of the left side of the septum it is below the membranous septum and separated from the endocardium of the right side of the septum by a considerable thickness of myocardium and fibrous connective tissue. In cases like this the bundle is revealed by teasing away the superficial tissue of the uppermost part of the left side of the muscular septum.

Even when the bundle lies entirely within the membranous septum, the exposure from one side may be easier than from the other. The membranous septum varies considerably in thickness and is sometimes quite tough. In some cases the bundle is superficial on one side of a thick, tough, membranous septum, whereas exposure from the other side necessitates tearing away a considerable thickness of resistant fibrous tissue. It is advisable to examine both sides of the septum carefully and to proceed with the dissection cautiously until the most desirable approach is established.

In both fixed and fresh hearts the bundle is paler than the adjacent myocardium. In fixed hearts it is gray, white, or pale yellow, whereas in fresh hearts it often has a pale pink or violet hue. In some fresh hearts fine vessels may be seen to accompany the bundle. The commonest shape of the bundle is a more or less flat band with the thin dimension perpendicular to the face of the septum. Sometimes it is more rounded and thicker so that it would be oval on cross section. Occasionally it is roughly prismatic with one side lying on top of the muscular portion of the interventricular septum. The width of the bundle varies from approximately 0.7 to 3.5 mm., with an average of 1.8 millimeters. Since there is no sharp demarcation of the bundle where it blends with right atrial myocardium (see below), measurements of its length can only be approximate. Measured as well as possible from the most dorsal point where the bundle could be described as a distinct entity to the point of bifurcation (see below), the length of the atrioventricular bundle ranges between 7.0 and 15.0 mm., with an average of 11.3 millimeters.

The bundle may be traced back dorsally through a variable extent of membranous septum and then through the central fibrous body, or it may be followed into the latter directly from the upper part of the muscular septum. The central

fibrous body is often very tough and almost cartilaginous. When the bundle is traced backward or dorsally in this manner it is seen that it definitely crosses the line of attachment of the medial cusp of the tricuspid valve and passes into the right atrium. To follow it further in the right atrium a thin covering layer of subendocardial atrial muscle must usually be removed. There may be some fat in this region. The bundle definitely blends with the right atrial tissue in the region just above the attachment of the medial cusp of the tricuspid valve and a short distance ventral to the coronary sinus (Fig. 4).

The failure to demonstrate the atrioventricular bundle in a few of the dissections may be attributed to the inherent technical difficulties or possibly to unrecognized anatomic variations. Except for its possible rare absence as a congenital anomaly the bundle seems to be a constant structure.

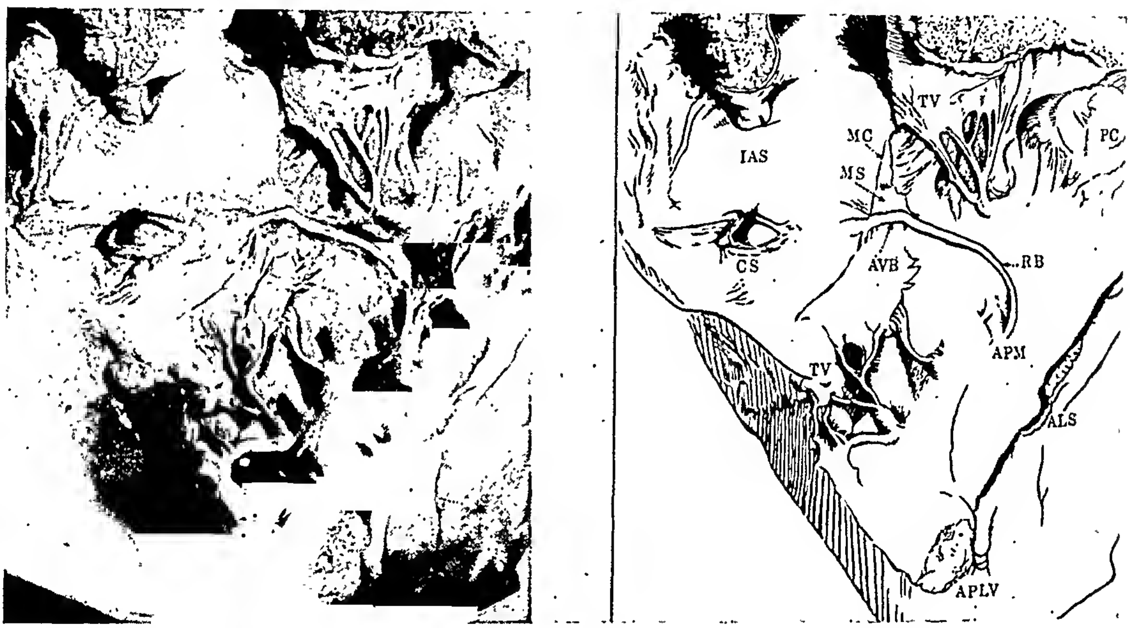

Fig. 4.—Photograph and labeled diagram of dissection of the atrioventricular bundle (bundle of His) and right branch of normal adult human heart (approximately × 3/4). Looking into the right ventricle and facing the right side of the interventricular septum. *ALS*, anterior longitudinal sulcus; *APLV*, apex of left ventricle; *APM*, base of anterior papillary muscle or right ventricle; *AVB*, atrioventricular bundle (bundle of His); *CS*, orifice of coronary sinus; *IAS*, interatrial septum; *MC*, line of attachment of medial cusp of tricuspid valve; *MS*, membranous portion of interventricular septum; *PC*, cusp of pulmonary valve; *RB*, right branch of atrioventricular bundle; *TV*, medial cusp of tricuspid valve. A part of the medial cusp of the tricuspid valve which covered the membranous septum and the bundle has been removed.

The Atrioventricular Node (*Node of Tawara*).—Demonstration of the atrioventricular node as a structure with more or less clearly defined boundaries was possible in only a few dissections. The failure to demonstrate a sharply delimited node in most instances by the method of dissection used must be correlated with a study of the serial sections. It was demonstrated in the serial sections that when viewed in cross section the node appears as a distinct entity (Figs. 1 and 3,*A*). In the dissection, however, one looks down on the subendocardial side of the node, and here apparently there is usually no sharp demarcation at the sites of blending with atrial muscle and bundle of His. This may be appreciated

to some extent by examining Fig. 1. If one imagines approaching this node from the endocardium by dissection, one can see how the subendocardial side of the node might be perfectly flush with adjacent atrial myocardium. The circumscribed character of the node is more apparent in a plane perpendicular to that viewed in the dissection, a plane such as is illustrated in Figs. 1 and 3,*A*. The side of the node itself may be marred in being exposed, since in removing the subendocardial atrial muscle that covers it, connections between it and the subendocardial muscle must be torn.

The Right Branch.—The bundle can be traced ventrally directly into the right branch (Fig. 4). The latter may be followed in a curved course on the right side of the septum from its origin to the base of the anterior papillary muscle. The muscle of the septum along which the right branch runs is often raised into a ridge of variable prominence which is known as the septal trabecula or moderator band. The proximal portion of the right branch is usually immediately subendocardial. After a short distance it gradually comes to lie deeper in the myocardium. The most distal visible portion becomes superficial again near the base of the anterior papillary muscle and frequently widens and fans out. Like the bundle, the right branch is paler than the adjacent myocardium. It often looks very much like a fine nerve after it is exposed by dissection. The bundle and right branch were always visible to the naked eye after exposure. In some cases, however, they were extremely thin, particularly the right branch, and in these cases it is doubtful if exposure would have been possible by dissection without magnification.

The proximal part of the right branch and the most distal part grossly demonstrable are often visible without magnification and without dissection. From 1.5 to 2.9 mm. of the distal part was visible in various hearts where it appeared as a thin, gray subendocardial band or streak passing toward the base of the anterior papillary muscle. In one heart the entire right branch was visible without magnification and without dissection.

In most cases the right branch is given off from the bundle near the crest of the muscular septum and comes to lie subendocardially immediately. However, in a few instances in which the bundle lay on the left side of the septum and the bifurcation was below the crest of the septum, the right branch had to be traced through the muscle of the upper part of the interventricular septum.

The right branch is usually a more or less rounded, narrow band with the cross section of a flattened oval or circle. In some of the hearts the distal part of the right branch was inadvertently cut by the pathologist in opening the heart, and in these hearts the branch can usually be followed to the cut end. In practically all of the remaining hearts in which the branch had not been cut it can be followed as far as the base of the anterior papillary muscle where it can be traced no farther. In the latter hearts the distance that the right branch can be followed from the point of bifurcation of the atrioventricular bundle (see below) ranges from 23.0 to 50.0 mm., with an average of 38.9 millimeters. The width of the right branch varies from approximately 0.3 to 2.7 mm., with an average of 1.0 millimeter. Usually the branch is wider at its origin and then narrows down.

Sometimes the terminal visible portion at the base of the anterior papillary muscle widens out again.

The Left Branch and the Bifurcation.—The dissection of the bifurcation and the beginning of the left branch is best carried out after the bundle of His and the right branch have been exposed. The best approach is from above. The structures above the bundle are carefully cut away, and the septum is mounted under the microscope in such a way that one is looking down on the crest of the septum. If the tissue on the left side of the bundle is now carefully teased away from above downward, it can be demonstrated in most cases that the bundle sends off a series of fibers or a very thin sheet of muscle to the left side of the septum. When the dissection is successfully carried far enough ventrally along the upper part of the septum a distinct inverted V can be made out, one arm of which is formed by the right branch and the other by the ventral margin of the left branch (Fig. 5). The apex of the V was taken as the point of bifurcation in measuring the lengths of the bundle of His and of the right branch. Actually, fibers of the left branch are given off for some distance dorsal to this point, in one case over a distance of as much as 9.0 millimeters. The V is usually near the ventral margin of the membranous portion of the interventricular septum.

While the origin of the left branch is quite distinct and the branch could be followed for a short distance, it was not possible to dissect it very far down the septum without tearing it. The left branch is thinner than the right. Its fibers are intimately connected with the endocardium, and they tear easily when an attempt is made to separate them from the endocardium. It was not possible to expose the entire left bundle branch and its divisions as illustrated in one of the standard anatomy texts.[43]

THE QUESTION OF ACCESSORY ATRIOVENTRICULAR MUSCULAR CONNECTIONS

At the height of the controversy between the proponents of the neurogenic and the myogenic theories at the end of the last century, Kent's study on atrioventricular muscular connections in mammalian hearts appeared.[41,a] It was the first demonstration of such connections and described them in several regions of the hearts of various newborn and older animals. His,[1] in a study which appeared immediately following that of Kent in the same year, described and localized the single atrioventricular muscular bundle which now bears his name. Kent maintained in later papers that the concept of a single atrioventricular connection was erroneous, that there were other atrioventricular connections besides the bundle of His, and that, in particular, there was one in the right lateral portion of the human heart.[44,a-g] The latter has become known as the bundle of Kent. Other investigators have stated also that there are multiple atrioventricular connections.[34,39]

A thorough search for atrioventricular muscular connections requires the study of large numbers of serial sections. Three such detailed studies have recently been made of human hearts in cases in which the electrocardiogram showed the syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). In one case Wood, Wolferth, and Geckeler[45] found several

atrioventricular connections in the general region designated by Kent. In the second case, Oehnell[46] found no muscular connections between the right atrium and right ventricle, but did locate an atrioventricular bundle in the posterior wall of the heart connecting the left atrium and left ventricle. In the third case, Deerhake, Kimball, Burch, and Henthorne[47] found one connection on the right side of the heart and one on the left.

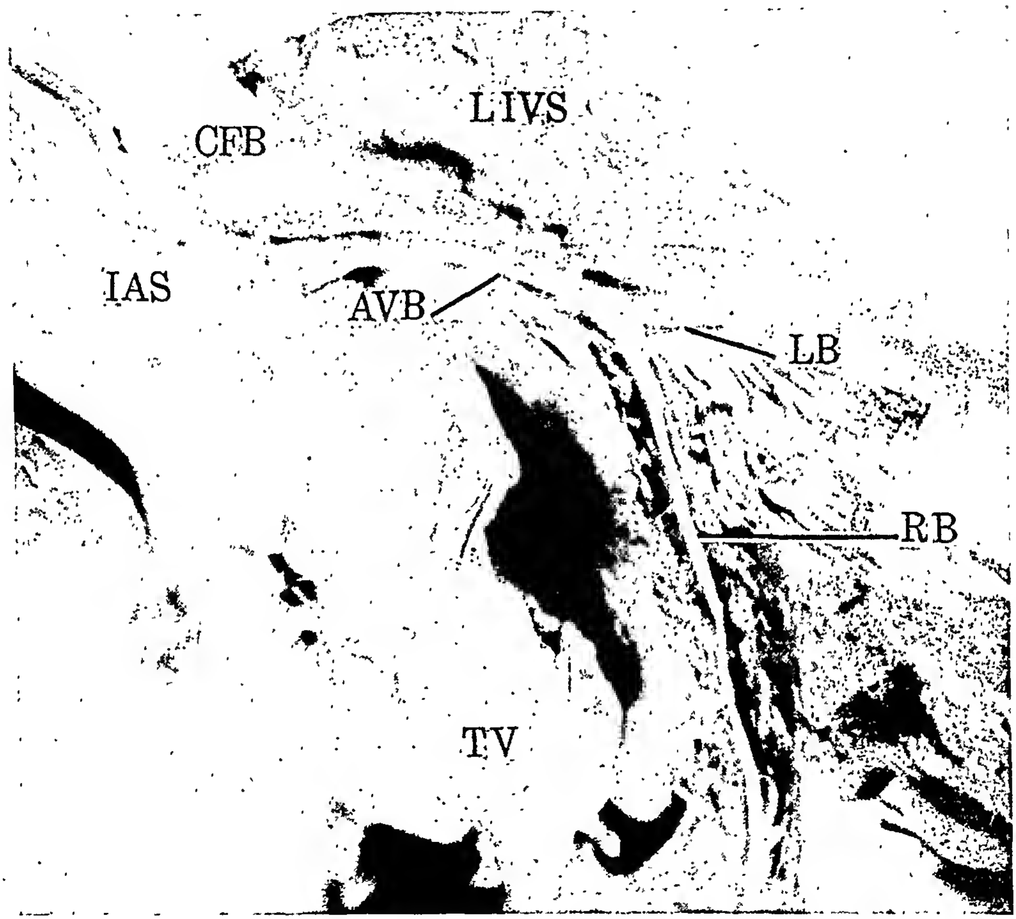

Fig. 5.—Photograph of dissection of atrioventricular bundle (bundle of His) and its bifurcation, normal adult human heart, (approximately × 4). Looking down on the crest of the interventricular septum. The structures above the crest of the septum have been removed. *AVB*, atrioventricular bundle (bundle of His); *CFB*, central fibrous body; *IAS*, interatrial septum; *LB*, left branch of atrioventricular bundle; *LIVS*, left side of interventricular septum; *RB*, right branch of atrioventricular bundle; *TV*, medial cusp of tricuspid valve.

In the present investigation the atrioventricular junctions of four normal human hearts were carefully searched by serial sections, in two of the hearts completely around both atrioventricular orifices, in a third completely around the mitral orifice, and in a fourth in a number of regions about both atrioventricular orifices. In none of the hearts were any muscular atrioventricular connections found other than the bundle of His. The atrial and ventricular muscle fibers are sometimes very close to each other at the atrioventricular junction, but they are

always separated by a layer of fibrous tissue of varying thickness, and careful study of serial sections reveals no continuity of muscle fibers from atrium to ventricle. It is possible that by studying only every tenth section in the adult hearts some small connections were overlooked. It is possible, also, that because of scattered, unsatisfactory sections in both the adult and the newborn hearts such small connections were overlooked. Nevertheless, in the thousands of sections studied no evidence of accessory muscular connections was found.

Anomalous Atrioventricular Excitation (*Wolff-Parkinson-White Syndrome*).—These observations may have some bearing on one of the hypotheses which has been advanced to explain the syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome). It has been postulated that this syndrome arises from the existence of anomalous atrioventricular muscular pathways through which premature excitation of the ventricle occurs.[48] While such connections have been histologically demonstrated in a few cases of this syndrome,[45,46,47] it has not been entirely clear whether such connections exist also in the hearts of individuals with normal atrioventricular conduction. If these connections are found to be absent in most normal human hearts, then a normal control for the hypothesis will be available. The presence of accessory connections in the cases of anomalous atrioventricular excitation would then assume added importance.

To be sure, the hypothesis is still tenable if accessory atrioventricular connections are found more frequently than only in cases of the Wolff-Parkinson-White syndrome, provided that the connections are always found with the syndrome. It may be maintained that the accessory pathways are necessary to produce the syndrome, but that they do not always function, and that their mere presence, therefore, does not insure the existence of anomalous atrioventricular conduction. The hypothesis must, in fact, postulate that the pathways sometimes do not function since in individuals with the Wolff-Parkinson-White syndrome, anomalous conduction may be apparent only at times, and at other times conduction may be normal. Admittedly, however, the hypothesis would be more convincing if the anomalous connections were absent in most normal hearts and were invariably associated with the syndrome. Much further investigation will be required to determine whether or not this is so.

Another type of possible accessory pathway which may conceivably be involved in anomalous atrioventricular excitation is one from the atrioventricular node or bundle directly to septal myocardium, by-passing the main bundle branches. Such connections were observed by Mahaim[41] and by Robb and Turman,[42] and one was present in the heart of the newborn infant reported here. How frequent such connections are and what their significance is requires much further investigation. They have not been mentioned in the few cases of anomalous atrioventricular excitation in which histologic studies were carried out.

Nerve Elements.—In many regions widely distributed about both atrioventricular rings, nerve ganglion cells and nerves were observed at the atrioventricular junction. The extrinsic and intrinsic nerve supplies of the hearts of man and other animals have been studied by several investigators.[22,36,49-58] By

suitable techniques some of these investigators traced nerve endings to myocardial fibers as well as to the sinoatrial node, the atrioventricular node, and the bundle of His. The nervous influence on atrioventricular conduction, particularly the vagal influence, is very well known, and the demonstrated nerve endings in the nodes and bundle have generally been regarded as serving the function of modifying the activity of the muscular atrioventricular conduction system.

It is not within the scope of this paper to consider the experimental and pathologic evidence for and against the myogenic and neurogenic theories of cardiac conduction. The object of this study has been simply to examine the contention that there is no anatomic basis for the myogenic theory.[35] Evidence has been presented which corroborates the opinion of most students of the subject that there is a sound anatomic basis for the myogenic theory of atrioventricular conduction.

SUMMARY AND CONCLUSIONS

1. The widely accepted concept of the atrioventricular muscular conduction system of the human heart has recently been challenged. The present microscopic and macroscopic studies do not confirm the anatomic observations on which the criticism is based.

2. As has been demonstrated by previous investigators, there is normally a constant atrioventricular muscular bundle (bundle of His) located at the cephalic end of the interventricular septum which originates in a distinct atrioventricular node (node of Tawara) and divides into left and right bundle branches. The atrioventricular node has a number of connections with atrial muscle. These relations are described and illustrated.

3. A systematic search in a few normal hearts fails to reveal any atrioventricular muscular connections other than the bundle of His.

4. The syndrome of anomalous atrioventricular excitation (Wolff-Parkinson-White syndrome) has been explained by the existence of accessory atrioventricular muscular connections through which premature ventricular excitation occurs. This hypothesis has been supported by the histologic demonstration of such connections in a few cases, but there is inadequate information about normal hearts for comparison.

5. Another type of possible accessory muscular pathway was observed in the heart of a newborn infant leading from the bundle of His directly to septal myocardium and by-passing the main bundle branches. Such muscular connections have been previously described in studies of random hearts. They have not been mentioned in the few cases of anomalous atrioventricular excitation in which histologic studies were carried out, and their significance requires further investigation.

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EXPERIMENTAL STUDIES ON THE VALIDITY OF THE CENTRAL TERMINAL OF WILSON AS AN INDIFFERENT REFERENCE POINT

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THE central terminal method of Wilson[1] has been the most widely discussed means to free the precordial electrocardiogram from the electrical influence of the "indifferent" electrode when the latter is placed on one of the extremities. Universal acceptance of this method, however, has been withheld because its validity is based, in turn, on the validity of the classical Einthoven equilateral triangle hypothesis.[2] There can be no disagreement with the electrical scheme of Wilson (based on Kirchhoff's law) in so far as it results in a common terminus, the potential of which is equal to the algebraic mean of the potentials of the right arm, left arm, and left leg.[1] However, the central terminal becomes a truly indifferent reference point (zero potential) only when the sum of the potentials of the right arm, left arm, and left leg (the apices of the triangle) is equal to zero.[1] When the assumptions underlying the Einthoven theory are accepted without reservation, it can be shown mathematically that the sum of the potentials of the right arm, left arm, and left leg does equal zero.[3] It has been recognized by Einthoven,[4] as well as his more recent exponents,[5,6] that these assumptions were only "first approximations of the truth."[6] It has been necessary, therefore, to subject both the Einthoven hypothesis and its practical application to experimental analysis in order to determine the magnitude of the error involved in the basic assumptions.

The studies designed to determine the validity of the Wilson central terminal as a truly indifferent reference point may be divided into two main categories: (1) experiments testing the accuracy of the Einthoven equilateral triangle hypothesis, its individual assumptions or the theory as a whole, and (2) experiments determining the potential of the central terminal directly by comparing it with reference points which were considered to be truly indifferent (zero potential) by construction. These studies have been recently reviewed in part by Wilson and his associates[6] and may be interpreted briefly as follows:

1. The original Einthoven assumption that the heart may be considered electrically equivalent to a small dipole has been modified in the sense that a battery analogy would be more in accord with the facts and would avoid oversimplification.[7,8] This modification does not compromise the original theory

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since in either case, at any instant, the algebraic sum of the differences in potential existing in the heart can be treated as a vector and projected on the frontal plane of the body. The experiments which have attempted to determine whether or not the body may be considered a homogeneous volume conductor have yielded conflicting results.[9-16] The anatomic assumptions of the Einthoven theory involve an obvious and variable error,[6,17] the magnitude of which has not been directly determined. The results of experiments examining the Einthoven theory as a whole have been more uniform in indicating that a reasonably close agreement exists between the observed facts and the predictions of the theory.[6,18] However, here, too, there is difference of opinion.[19,20]

2. The direct measurements of the potential of the central terminal are of greater and more immediate interest since they determine the error of a method, the theoretical background of which is only approximately sound. The principal of these experiments has been the comparison of the difference in potential between fixed points on the body surface and the Wilson central terminal, on the one hand, and a reference point considered to be truly indifferent by construction, on the other. In addition, measurements have been made of the difference in potential between the Wilson central terminal and the truly indifferent reference point. In three of these experiments,[6,21,22] the subjects were immersed in water (distilled, tap, or lake). Eckey and Fröhlich[21] and Burger[22] used the bounding metal screen as the reference point of zero potential, whereas Wilson[6] placed his indifferent electrode in the lake water eleven feet from the immersed subject. The validity of these experiments in providing truly indifferent reference points has been discussed at length by Wilson[6] and by Wolferth and Livezey[20] and need not be reviewed here except by comment that while these reference points may not necessarily be at zero potential, they are sufficiently indifferent, especially when the reference electrode is placed at a relatively great distance from the heart. Viana[23] studied this problem by constructing a large equilateral triangle and placing the subject in the center. The triangle and subject (rabbit and man) were placed on moist ground and wires were led to a common terminus from three electrodes imbedded in the ground at the apices of the triangle. This terminus was used as the indifferent reference point. The results of these experiments have shown, with one exception, that: (1) The difference in potential between fixed points on the body surface and the indifferent reference point was greater than the difference in potential between the Wilson central terminal and the indifferent reference point. (2) The potential of the Wilson central terminal (when paired to the indifferent reference point) was not consistently zero, but ranged from 0.15 to 0.36 millivolt. In the single experiment which Wilson performed,[6] the difference in potential between the left leg and the indifferent reference point in the lake was less than the difference in potential between the central terminal and the distant reference point. This indicated that in this subject the left leg was more indifferent than the Wilson central terminal. This may have been a rare phenomenon as was suggested,[6] but if it were to occur sufficiently frequently, it would obviously destroy the purported advantage of the central terminal over the extremities as the ideal location for the distant electrode. The observation of Wilson has prompted us to re-

examine experimentally the validity of the central terminal as a null reference point. The experiments to be described are modifications of the immersion studies which have been referred to.[6,21,22]

MATERIAL AND METHOD (Illustrated in Fig. 1)

Normal adult men were placed in a tile-lined indoor swimming pool, 75 feet by 24 feet, containing chlorinated tap water (0.86 parts per million). The subjects were upright and immersed to such a depth that the water level reached to, and included the chin or lips. The subjects could be so positioned that they were approximately equidistant from the two ends and from the two sides of the pool. An equilateral triangle, each side of which was ten feet long, was built of three narrow planks of light wood. A ten-foot length of No. 18 braided copper wire, insulated except at its ends, was fixed with adhesive tape at each apex of the wooden triangle so that eighteen inches of wire were suspended directly into the water below its surface. To the tip of each of the immersed wires was attached a German silver electrode measuring 2 inches by 1.5 inches (*E*). These three submerged electrodes formed the apices of a horizontal equilateral triangle (*EEE*) eighteen inches below the surface of the water, each side of which was ten feet long and the plane of which passed approximately through the apex of the heart. The free ends of the three wires were joined and inserted into one post of a double binding post electrode (CT_E). The other binding post of CT_E was used whenever this external central terminal was connected to the electrocardiograph. The terminal CT_E was taped in place on a small block of wood encased in rubber sheeting which, in turn, was fixed in place on one of the sides of the wooden triangle. This arrangement prevented immersion of the terminal. The wooden triangle was floated into position so that its apices were equidistant from the centrally placed subject and anchored with lengths of thin cord to fixed objects on the sides of the pool. Each apex of the triangle was approximately seven feet from the nearest side of the pool. Throughout the experiments the central position of the subject was checked closely.

A plank of wood approximately one foot wide and eight feet long was arranged at one side of the pool in the form of a diving board which extended out to and faced the subject. The segment which rested on the side of the pool was held in place with the electrocardiograph (*ECG*). To the end of the segment extending over the water was fixed a specially constructed junction box (*JB*) to which was connected the patient lead wire cable (*PLW*). A chest lead wire (*CLW*) fifteen feet long was inserted into a separate binding post on the junction box.* When properly connected, this long chest lead wire substituted for the ordinary chest lead wire on the patient lead wire cable and could also be used (IP_E) to connect a distant point *E′* (consisting of a German silver electrode like those forming the equilateral triangle, *EEE* in the pool) with the electrocardiograph. A long wire also attached to the junction box was suspended on the surface of the water ten to thirteen feet from the subject and served as a ground wire (*GW*), being

*We are indebted to Dr. A. Miller of the Sanborn Co., Cambridge, Mass., for his advice on the construction of the special equipment used in these experiments.

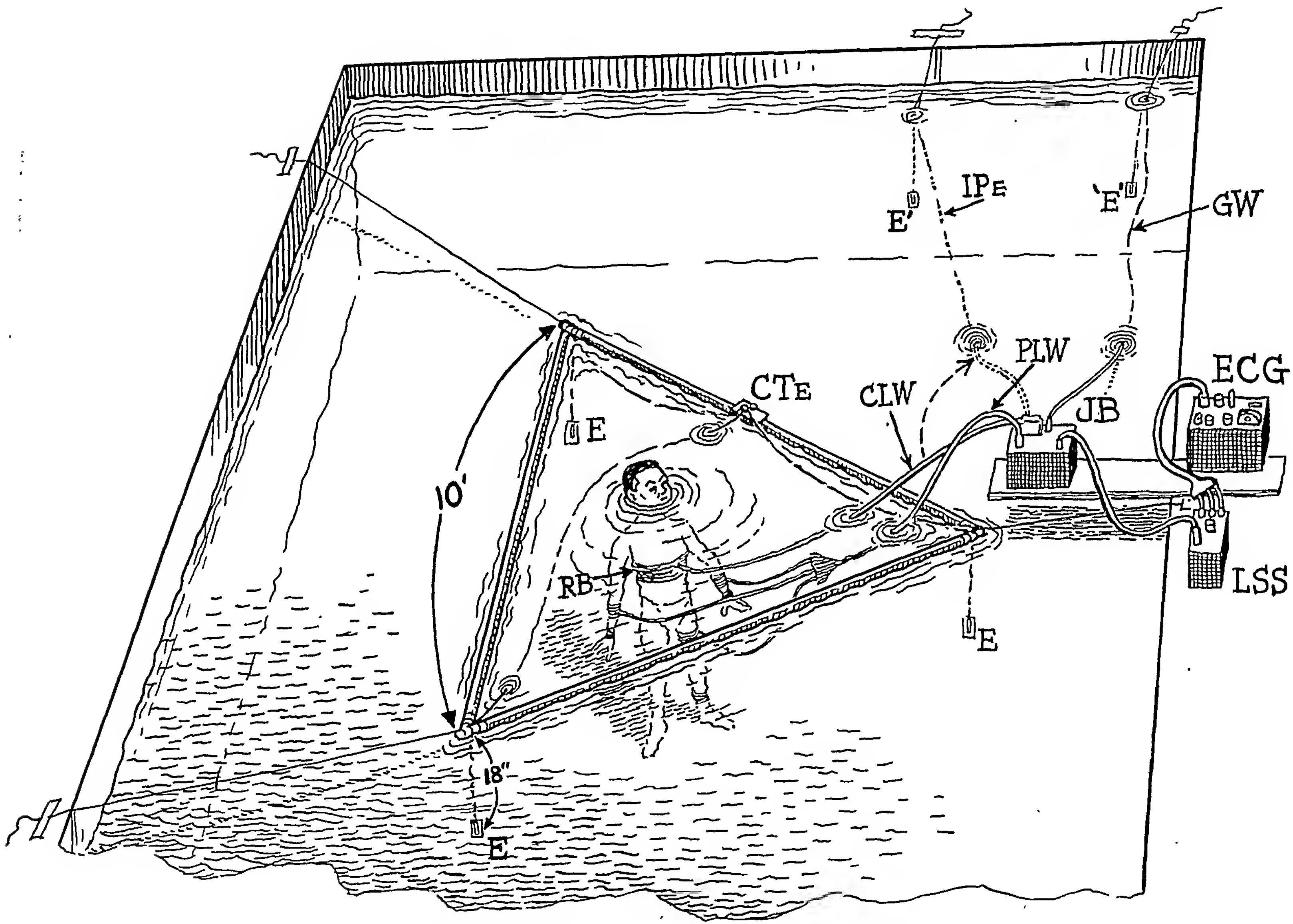


Fig. 1.—A diagrammatic representation of the arrangements and equipment used in the experiments. Discussed in text.

connected to a ground electrode '*E*'. The junction box was connected by an extension cable to a standard lead selector switch box (*LSS*) on the side of the pool; this switch was connected, in turn, to a vacuum tube amplifier type of electrocardiograph (Sanborn) in the usual manner. A switch on the instrument panel of the electrocardiograph facilitated reversal of polarity without the need for changing the actual wire connections in the machine. Two electrodes each were placed on the right arm, left arm, and left leg of the subject. A perforated rubber belt (*RB*) was placed around the chest of the subject allowing two chest electrodes to remain fixed in place without manual aid. One electrode was located in the fourth intercostal space just to the left of the sternum (which we labelled C_a) and the other was located in the left anterior axillary line at the same horizontal level as the first chest electrode (labelled C_b). Once immersed, the subject accomplished all changes in the location of the lead wires without assistance. Electrocardiographic records were also obtained when the subjects were on land at the usual standardization (1 mv. equals 1 cm. deflection). Records with the subjects immersed in the pool were taken at the maximum sensitivity of the machine (1 mv. equals 2 cm. deflection).

The following leads were recorded in each experiment and are so labelled in Figs. 2 to 4:

I. Before immersion; labelled *L* for land, (subject standing)
- A. Standard limb leads I, II, III
- B. Extremity leads
  1. Right arm (RA) minus Wilson central terminal (CT_W)
  2. Left arm (LA) minus CT_W
  3. Left leg (LL) minus CT_W*
- C. Precordial leads
  1. Chest electrode at fourth left parasternal intercostal space (C_a)
     - a. C_a minus RA
     - b. C_a minus LA
     - c. C_a minus LL
     - d. C_a minus CT_W†
  2. Chest electrode at left anterior axillary line (C_b)
     - a. C_b minus RA
     - b. C_b minus LA
     - c. C_b minus LL
     - d. C_b minus CT_W†

II. During immersion; labelled *W* for water, (subject standing):
- A. Standard limb leads I, II, III
- B. Extremity leads
  1. RA minus CT_W
  2. LA minus CT_W

*I, B 1, 2, and 3 are, respectively, V_R, V_L, and V_F.
†I, C 1 a, b, c, and d and I, C 2 a, b, c, and d are, respectively, C_R, C_L, C_F, and V leads.

3. LL minus CT_W
4. RA minus constructed external central terminal (CT_E)
5. LA minus CT_E
6. LL minus CT_E

C. Precordial leads

1. Chest electrode at Position C_a

   a. C_a minus RA
   b. C_a minus LA
   c. C_a minus LL
   d. C_a minus CT_W
   e. C_a minus CT_E

2. Chest electrode at Position C_b

   a. C_b minus RA
   b. C_b minus LA
   c. C_b minus LL
   d. C_b minus CT_W
   e. C_b minus CT_E

D. CT_W minus CT_E

In four experiments the long chest lead wire was fixed in place in the water thirteen to fourteen feet from the subject, connected with a submerged electrode, and was then considered as an external indifferent reference point (IP_E). The water depth at Point IP_E was three to four feet and the electrode was suspended one foot below the surface. In these four experiments the following additional leads were taken with the subject still immersed:

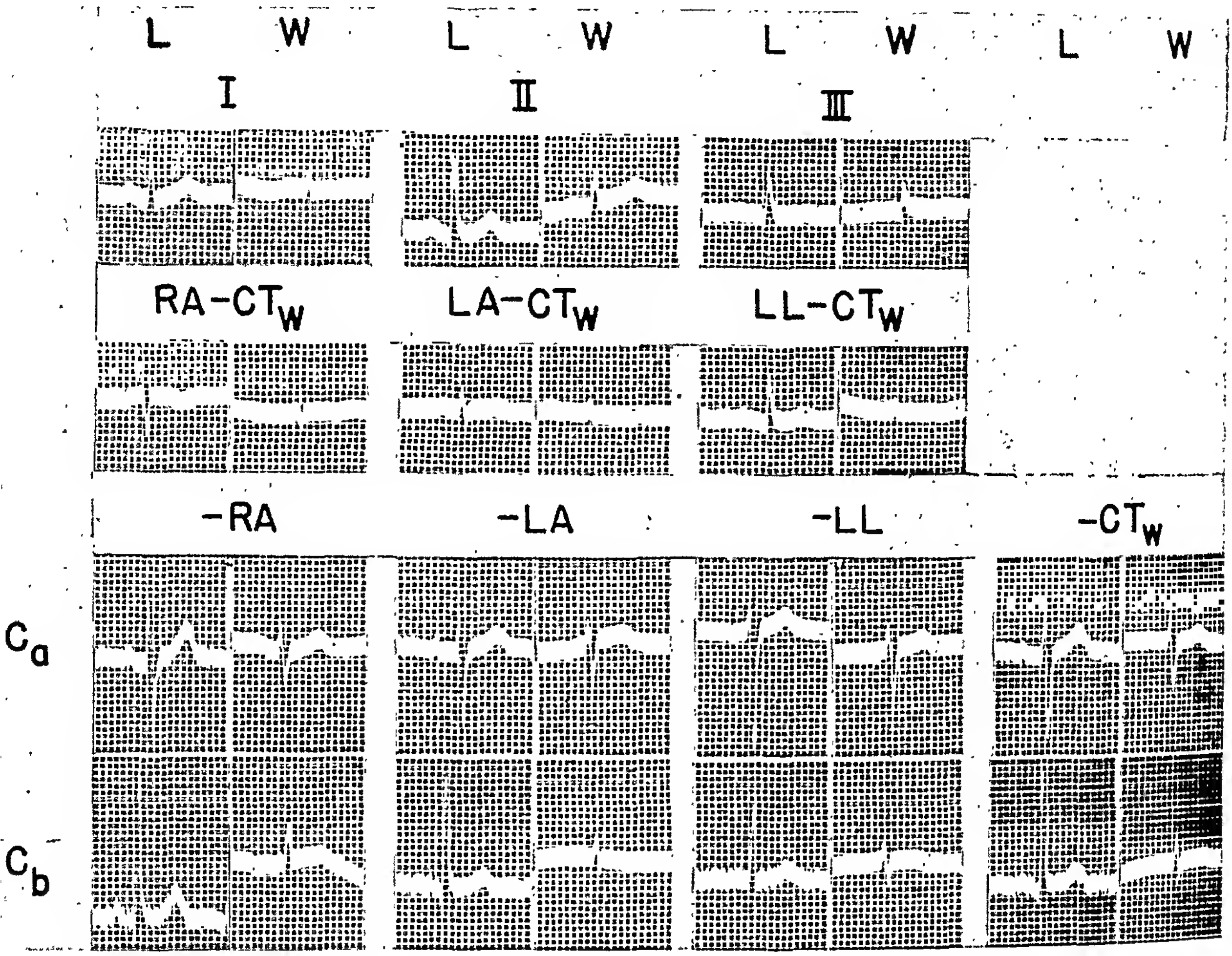
1. RA minus IP_E
2. LA minus IP_E
3. LL minus IP_E
4. C_a minus IP_E
5. C_b minus IP_E
6. CT_W minus IP_E

RESULTS

Nine experiments were performed. It was necessary to discard two of these because of somatic tremors, alternating current, and other artefacts. The results presented are based on the remaining seven experiments. The short circuiting effect of the water caused marked reduction of the amplitude of the deflections so that even with double standardization the deflections in water were about 20 to 30 per cent of their size on land. A complete experiment is reproduced in Fig. 2. The marked shunting effect encountered in water is exemplified in Fig. 2,*A*.

The results may be summarized under five headings:

1. The difference in potential between any of the three extremities and either the external central terminal or the external indifferent reference point in the water was greater in all experiments than the difference in potential between the Wilson central terminal and either of these reference points (Fig. 2,*B*). Hence, on the basis of these experiments, the potential of the Wilson



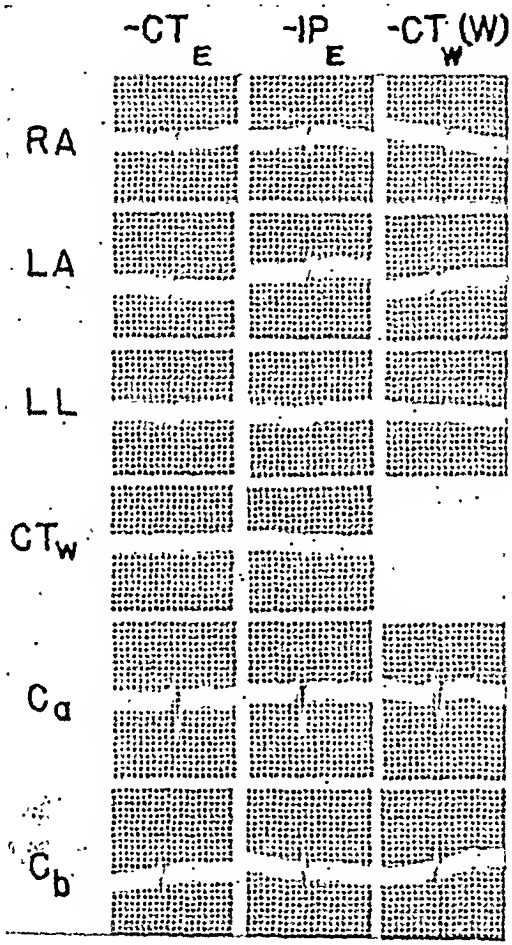
A.

Fig. 2.—An example of a complete experiment. The symbols used are explained in the text.

A, The vertical columns *L* and *W* indicate the records taken, respectively, on land and water. Each lead is identified by symbols at the top of the segments of the record. However, in the case of the chest leads, the chest position is indicated at the left of the row of strips and the reference point at the top of the vertical column. In spite of a standardization of 1 mv. = 2 cm. when the subject was immersed, the amplitude of the deflections is much smaller than before immersion with a standardization of 1 mv. = 1 cm.

B, The lead connection of each lead shown is identified by the lettering at the left of each horizontal row and the heading of each vertical column. The difference in potential between each extremity and either external reference point is greater than the difference in potential between the respective external reference point and the Wilson central terminal. In this case, Lead $LA - CT_E$ resembles $CT_W - CT_E$ more closely than $RA - CT_E$ and $LL - CT_E$. This figure also illustrates the deflections obtained when each of the two chest positions (C_a and C_b) was paired, in turn, with CT_E, IP_E, CT_W. These three reference points gave practically identical records. (*W*) in the third vertical column indicates that the records in this column were taken when the subject was immersed. Discussed in text.

central terminal must be considered more nearly like that of the null reference points than that of any extremity. Similarly, the Wilson central terminal must be considered more indifferent than the right arm, left arm, or left leg. In no instance did we observe a smaller potential difference between any extremity and the external central terminal than between this central terminal and the Wilson central terminal. The same results were obtained when IP_E was used as the indifferent reference point.

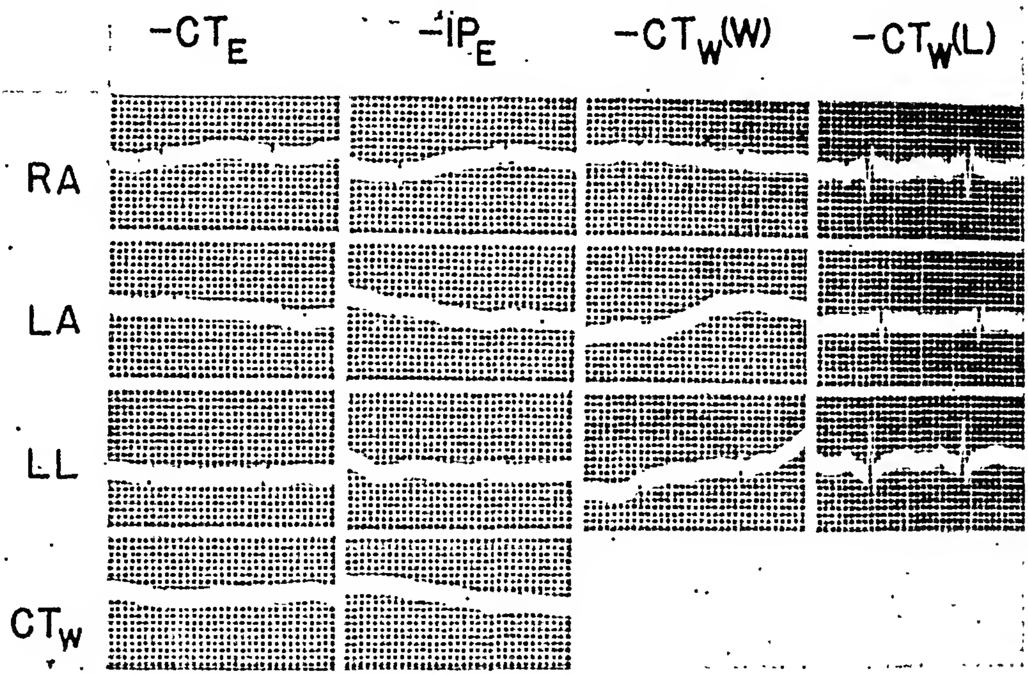


B.

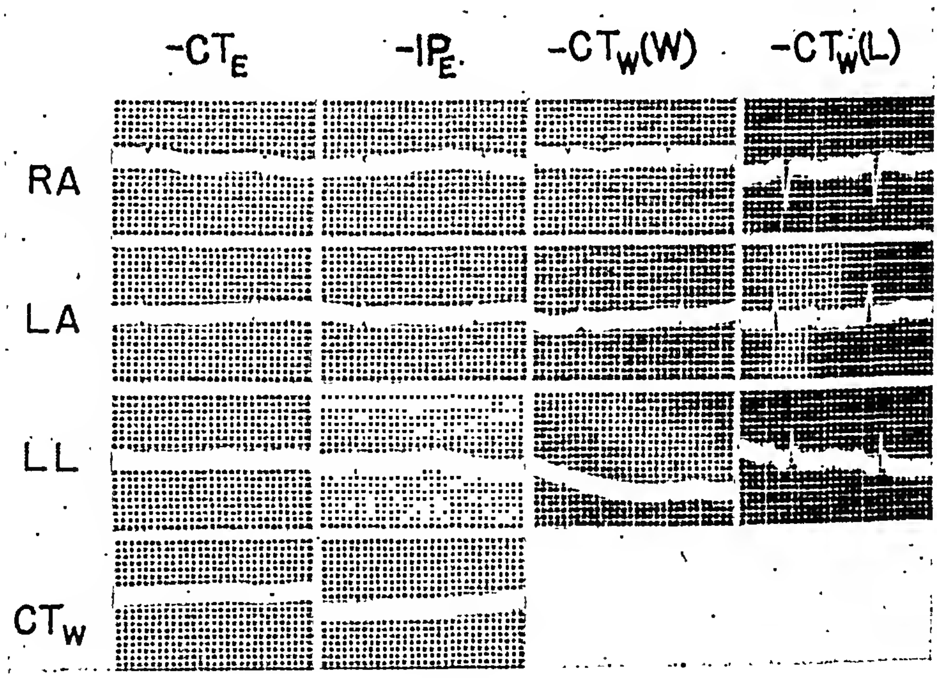
Fig. 2. (Cont'd).—*See opposite page for legend.*

2. In two experiments there was no recorded difference in potential between the Wilson central terminal and the external central terminal (Fig. 4,*A*). In the remainder there was a small difference of potential, the Wilson central terminal being slightly negative in relation to the external central terminal in all but one experiment (Figs. 2,*B* and 4,*B* and *C*).

3. In the electrocardiograms which showed small deflections when the left arm was paired with the external central terminal and relatively tall upright



A.



B.

Fig. 3.—Two additional examples of the potential difference obtained when each of the three extremities was paired, in turn, with CT_E, IP_E, and CT_W. The symbols used are explained in the text. (*W*) and (*L*) in the third and fourth vertical columns represent, respectively, the extremity leads taken in water and on land. The latter records are shown for comparison with the former.

A, The Wilson central terminal is slightly negative to each external reference point. The difference in potential between *LA* and CT_W or either external reference point resembles the potential difference between CT_W and either external reference point more closely than does the difference in potential between *RA* or *LL* and these points.

B, The Wilson central terminal is at the same potential as each of the external reference points. The potentials of *LA* and *LL* are approximately the same and more like that of CT_W than *RA*. (*W*) means subject immersed; (*L*), subject on land. Discussed in text.

deflections when the left leg was paired with the external central terminal, LA$-$CT$_E$ more closely resembled, but was not identical to, the potential difference between the Wilson central terminal and the external central terminal than did either of the other extremity leads, RA$-$CT$_E$ and LL$-$CT$_E$, (Fig. 3,*A*). In the electrocardiograms which showed small upright deflections in both LA$-$CT$_E$ and LL$-$CT$_E$, either LL$-$CT$_E$ or both LL$-$CT$_E$ and LA$-$CT$_E$ resembled CT$_W$$-CT_E$ (Fig. 3,*B*). Similar results were obtained when IP$_E$ was used as the indifferent point. Hence, as would be expected, the potentials of the extremities vary with the direction of spread of the impulse in the heart and the position of the heart in the thorax, and, depending on this position, the left arm or left leg may, at times, have potentials which are almost as small as those of the Wilson central terminal.

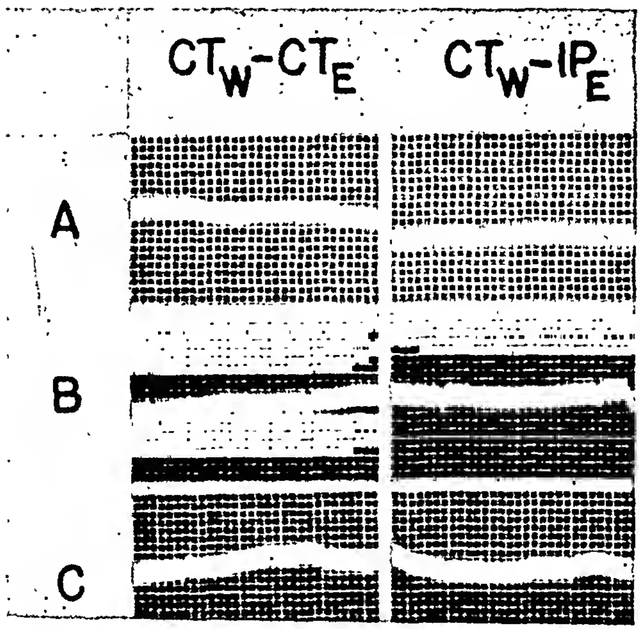


Fig. 4.—Three experiments in which the Wilson central terminal was paired, in turn, to the external central terminal (*CTE*) and the distant reference point (*IPE*). In *A*, the two external reference points have the same potential as the Wilson central terminal. In *B* and *C*, the two external reference points have potentials different from each other and from that of the Wilson central terminal. Discussed in test.

4. The deflections obtained by pairing each of the two fixed points on the chest with either the external central terminal (CT$_E$) or with the indifferent point in the water (IP$_E$) were identical to those obtained when these fixed points were paired with the Wilson central terminal. Similar results were also observed when the extremity leads were taken in the same manner. When slight differences existed they could be explained on the basis of the small potential of the Wilson terminal (Fig. 2,*B*). Precordial positions were selected in order to obtain larger deflections.

5. In four experiments it was possible to compare the potentials of the two indifferent points (CT$_E$ and IP$_E$) by pairing each with CT$_W$. In one experiment

both the external central terminal and the distant point in the water were at the same potential as the Wilson central terminal (Fig. 4,*A*). In three experiments a small difference was observed between $CT_W - CT_E$ and $CT_W - IP_E$, indicating that the two indifferent points were not constantly at the same potential (Fig. 4,*B* and *C*). Nevertheless, regardless of the type of reference point used (CT_E or IP_E), the potential of the Wilson central terminal was always more nearly like that of the reference point than the potential of any extremity (Fig. 2,*B*).

COMMENT

The principal limitation to the quantitative analysis of our data was the small size of the deflections resulting from the short circuiting effect of the water. It was felt that actual measurements of these small deflections would involve an error probably sufficiently large to invalidate the measurements themselves. Consequently, no quantitative data are given and no specific values are assigned to the potential variations of the Wilson central terminal when it was paired to external reference points. Nevertheless, qualitatively, the electrocardiograms can be interpreted without difficulty. The opinions of several independent observers who inspected the records were identical. We feel, therefore, that the results given are justified, especially since they represent some departure from previous views of the department from which this study comes.

As to the validity of the conclusion that the Wilson central terminal in these experiments was consistently more indifferent than any of the fixed points on the body surface, it is necessary to comment on the external central terminal (CT_E) which we used as the ultimate null reference point. It is apparent that our equilateral triangle was constructed in the horizontal plane of the body, whereas strict electrophysical theory would demand that the triangle lie in the same plane as the vector which expresses the heart's mean electromotive force. This plane forms an angle with the horizontal as well as the frontal planes of the body. Nor can we assume any strictly constant relationship between these two planes in view of the differences in position of the heart from subject to subject. Furthermore, the plane of our equilateral triangle did not divide the conducting medium (water) into two identical parts any more than does the Einthoven triangle in the frontal plane divide the body into two equal parts. However, as Wilson has pointed out,[6] the magnitude of the errors involved in these spatial arrangements decreases as the distance of the apices of the triangle from the heart increases. It is on the basis of the great distance of these apices from the heart that we, and presumably Viana,[23] considered the central terminal formed from the large external equilateral triangle as a valid indifferent reference point. We do not claim that the potential of our external central terminal is necessarily zero, but only that it is smaller than the potential of points on the body surface. The fact that similar results were obtained when our reference point was at a great distance from the heart, and not dependent on the position of the plane of the triangle, fortifies this view.

The results of our experiments confirm the work of previous investigators. It may be concluded, therefore, that the Wilson central terminal, while not con-

stantly at zero potential, is consistently more indifferent from subject to subject than any fixed point on the body surface. It follows that the errors inherent in the assumptions of the Einthoven equilateral triangle hypothesis are not sufficiently large to invalidate completely the theory on which this central terminal is based nor to interfere with the usefulness of the central terminal in clinical electrocardiography. It was previously noted that in some subjects the spread of the impulse through the heart and the position of the heart may cause either the left leg or the left arm to be almost as indifferent as the central terminal. Therefore, in such subjects a precordial lead obtained by placing the distant electrode on the left leg or left arm will be practically the same as the V (central terminal) lead. The advantage of the central terminal as a reference point lies in the fact that it is not dependent on any particular position of the heart, but rather that it remains more indifferent in a series of subjects than the extremities, irrespective of these variables.

SUMMARY AND CONCLUSIONS

1. The validity of the central terminal as a truly indifferent reference point has been re-evaluated in a series of immersion experiments. The potential of this central terminal was compared to two other reference points, considered to be indifferent by construction. The first was an external central terminal formed from a large submerged equilateral triangle, the apices of which were equidistant from the immersed subject. The second was a distant point under water thirteen to fourteen feet from the immersed subject.

2. The difference in potential between either of these reference points and the Wilson central terminal was consistently smaller from subject to subject than the difference in potential between each of five fixed points on the body surface and either external reference point or the Wilson central terminal. The five fixed points were the right arm, left arm, left leg, and two points on the anterior chest wall. The deflections obtained by pairing each of the five points with either external reference point were identical to or closely resembled the deflections obtained by pairing these points with the Wilson central terminal.

3. In two of seven experiments the Wilson central terminal and the external central terminal were at the same potential throughout the cardiac cycle. In the remainder, the Wilson central terminal was slightly negative (four experiments) or positive (one experiment) to the external central terminal. In one of four experiments the two external reference points were at the same potential, whereas in the remainder there was a slight difference.

4. The results confirm the experience of others and indicate that the Wilson central terminal may be considered a more uniformly indifferent reference point than any of the extremities.

We are indebted to the various house officers who submitted patiently as subjects for this study.

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POTASSIUM AUTOINTOXICATION FROM HEMOLYSIS OF RED CELLS

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It is generally known that in man and in certain species of animals there is a marked difference between the concentration of potassium in the plasma and that normally present in the erythrocytes.[1] In the latter, the amount of potassium is approximately twenty times greater than that found in the plasma. In recent years, there has been an increasing number of reports dealing with the syndrome of potassium intoxication, especially concerning the effects of high potassium on cardiac musculature. The present study was undertaken to determine if the sudden liberation of the intracellular potassium in conditions marked by rapid and extensive intravascular hemolysis of erythrocytes would be sufficient to cause or bring on the signs and symptoms of potassium intoxication.

Ringer[2] showed that excess of potassium caused the frog's heart to stop in diastole. In 1938, Winkler, Hoff, and Smith[3] produced potassium intoxication in dogs by the intravenous injection of isotonic potassium chloride and demonstrated a regular sequence of electrocardiographic changes characteristic of the various stages of this intoxication by which the syndrome could be recognized. These consisted, in succession, of progressive elevation of the T wave, which often becomes diphasic (serum potassium of 5.0 to 7.0 meq. per liter), depression of the S-T segment (8.0 to 10 meq. per liter), disappearance of the P wave (9.0 to 11.0 meq. per liter), widening of the QRS complex, indicating intraventricular block (10.0 to 12 meq. per liter), terminal disorganization of the entire QRS complex, and cardiac arrest (14.0 to 16.0 meq. per liter). In 1941, the same authors[4] noted that dogs made anuric by various means died of typical potassium intoxication, as shown by electrocardiographic and blood potassium studies. Since that time, various authors have reported the occurrence of a similar syndrome in man in uremia[5,7,8,10] and in crush syndrome.[9] The possibility of potassium intoxication due to hemolytic reactions has been suggested by Finch, Sawyer and Flynn.[8] Recently it was shown by Roos, Weisiger, and Moritz[11] that when pigs were severely and extensively scalded, lethal levels of potassium and electrocardiographic changes characteristic of this intoxication were obtained, mainly as the result of the destruction of the red cells.

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In the rabbit the serum potassium is approximately 4.0 meq. per liter, while the erythrocytes contain 106 meq. per liter. If the packed cell volume be taken at 40 per cent, it can be calculated that in the absence of diffusion out of the blood vessels, approximately 15 per cent of the red blood cells must be hemolyzed to raise the serum potassium from 4.0 to 15.0 meq. per liter. If, however, one assumes complete equilibrium between the intravascular and the extracellular fluid, it would require approximately 60 to 65 per cent hemolysis to produce the same elevation of serum potassium. Apparently, therefore, the level of the serum potassium reached will depend on the degree and rate of hemolysis, the extent of diffusion of the excess potassium into the extracellular fluid, and the ability of the kidneys to excrete it.

METHODS

Rabbits were employed because their serum and erythrocyte content of potassium are very similar to that found in man. They were anesthetized with Nembutal and in most of the experiments the constant administration of intratracheal oxygen was employed to maintain oxygen tension in the lungs in case of respiratory arrest. Electrocardiograms were recorded at frequent intervals from Lead II. Blood samples for potassium determinations were obtained by direct heart puncture at irregular intervals and at the time of death in most instances. The serum potassium was determined on ashed samples by the colorimetric method of precipitation of silver cobalti-nitrite in ethyl alcohol, and color development in ammonium thiocyanate.[17]

Several methods were used to lake red cells and release their content of potassium. (A) To produce intravascular hemolysis, a 1.0 per cent solution of saponin (Eastman Kodak) was injected intravenously into the femoral veins of twelve rabbits. The amount of saponin injected and the duration of the injection are indicated in Table I. Injection was discontinued when electrocardiograms began to show the final disintegration of the QRS complexes. Blood samples obtained were centrifuged immediately. In Experiments 3, 4, 5, 7, 19, and 21 (Table I) the withdrawn blood samples were placed immediately in graduated uniform bore "Fisher" tubes and packed cell volumes were determined after the blood was centrifuged at 3,000 revolutions per minute for fifteen minutes. No anticoagulants having been used, the packed cell volumes were determined on partially clotted blood. As a control study, the packed cell volume of normal rabbit's clotted blood was compared with that of citrated blood. (B) In an attempt to reproduce an incompatible transfusion reaction, fresh human citrated blood (Group O) was injected intravenously into one rabbit at the rate of 1.0 to 1.5 c.c. per minute until death occurred (Experiment 8, Table II). Human citrated blood (Group O) was hemolyzed completely by freezing and thawing and the laked mixture of blood was injected intravenously into two rabbits at slightly different rates until death occurred (Table II, Experiments 9 and 10). Packed cell volumes of the samples of heart's blood, withdrawn terminally, were determined in Experiments 8 and 10 by the same procedure described in (A). (C) Rabbit blood obtained from donor animals by complete exsanguination

TABLE 1. EFFECTS OF INTRAVENOUS INJECTION OF 1 PER CENT SAPONIN

EXP. NO.	WT.	AMOUNT INJECTED	DURATION OF INJECTION	TIME OF DEATH AFTER START OF INJECTION	CONC. OF POTASSIUM IN SERUM			DEGREE OF HEMOLYSIS		CHANGES IN ELECTROCARDIOGRAM			
					TIME SAMPLE TAKEN AFTER INJECTION	SAPONIN INJECTED	POTASSIUM CONC.	PACKED CELL VOLUME	HEMOLYSIS (CALCULATED)	T-WAVE ELEVATION	RS-T DEPRESSION	LOSS OF P WAVE	SPLIT OF QRS
	(KG.)	(C.C.)	(MIN.)	(MIN.)	(MIN.)	(C.C.)	(MEQ./L.)	(PER CENT)	(PER CENT)				
2	2.9	39.0	27	27	13	19.5	16.9	—	—	+	+	+	+
					27	39.0	16.5	—	—	+	+	+	+
3	4.7	33.5	55	60	30	31.5	7.6	23.0	42.5	+	+	−	−
					46	31.5	7.1	—	—	+	+	−	−
					60	33.5	8.5	24.0	40.0	+	+	+	−
4	3.6	20.0	10	30	19	20.0	17.5	14.0	65.0	+	+	+	+
5	3.6	14.5	6	12	12	14.5	15.0	35.0	12.5	+	+	+	+
6	2.4	13.8	36	36	—	—	—	—	—	+	+	+	+
7	3.3	30.0	8	20	20	30.0	14.5	14.0	65.0	+	+	+	±
13	4.1	32.0	17	45	12	30.0	12.5	—	—	+	+	+	−
					20	32.0	13.5	—	—	+	+	+	±
17	4.1	54.0	30	39	29	52.0	5.2	—	—	+	+	−	−
					39	54.0	8.9	—	—	+	+	±	−
18	3.0	29.0	4	4	4	29.0	13.3	—	—	+	+	±	−
19	3.7	30.0	35	65	65	35.0	14.9	25.0	37.5	+	+	+	+
20	4.1	27.0	20	20	—	—	—	—	—	+	+	+	±
21	3.7	43.0	31	31	6	10.0	11.7	28.0	30.0	+	+	+	−
					16	27.0	14.2	28.0	30.0	+	+	+	±
					21	32.0	20.0	26.5	33.5	+	+	+	+

Table II. Effects of Intravenous Injection of Human Fresh Blood and Human Laked Blood

EXP. NO.	WEIGHT (KG.)	SOLUTION INJECTED	AMOUNT INJECTED (C.C.)	DURATION OF INJECTION (MIN.)	RATE OF INJECTION (C.C./MIN.)	TIME OF DEATH AFTER INJECTION (MIN.)	DEGREE OF HEMOLYSIS: PACKED CELL VOLUME (PER CENT)	DEGREE OF HEMOLYSIS: HEMOLYSIS (CALCULATED) (PER CENT)	CONC. OF POTASSIUM IN SERUM: TIME SAMPLE TAKEN AFTER INJECTION (MIN.)	CONC. OF POTASSIUM IN SERUM: POTASSIUM CONC. (MEQ./1.)	CHANGES IN ELECTROCARDIOGRAM: ELEVATION OF T WAVE	CHANGES IN ELECTROCARDIOGRAM: RS-T DEPRESSION	CHANGES IN ELECTROCARDIOGRAM: LOSS OF P WAVE	CHANGES IN ELECTROCARDIOGRAM: SPLIT OF QRS
8	2.3	Citrated human blood (0)	17	19	1–1.5	19	0	100	19	38.2	+	+	+	+
9	3.2	Laked human red cells	31	15	2–4	15	—	—	—	—	+	+	+	+
10	3.1	Laked human red cells	28	24	1.5–2.5	24	15	62.5	24	18.8	+	+	+	+

TABLE III. EFFECTS OF INTRAVENOUS INJECTION OF RABBITS' LAKED RED CELLS

EXP. NO.	WEIGHT (KG.)	SOLUTION INJECTED	AMOUNT INJECTED (C.C.)	DURATION OF INJECTION (MIN.)	RATE OF INJECTION (C.C./MIN.)	TIME OF DEATH AFTER INJECTION (MIN.)	DEGREE OF HEMOLYSIS: PACKED CELL VOLUME (PER CENT)	DEGREE OF HEMOLYSIS: HEMOLYSIS (CALCULATED) (PER CENT)	CONC. OF POTASSIUM IN SERUM: TIME SAMPLE TAKEN AFTER INJECTION (MIN.)	CONC. OF POTASSIUM IN SERUM: POTASSIUM CONC. (MEQ./L.)	CHANGES IN ELECTROCARDIOGRAM: ELEVATION OF T WAVE	RS-T DEPRESSION	LOSS OF P WAVE	SPLIT OF QRS
22	4.7	Laked rabbit cells	90	35	2-3	35	—	—	14	12.4	+	+	+	∓
									30	19.9	+	+	+	+
									35	20.9	+	+	+	+
23	4.4	Laked rabbit cells	95	20	4-5	20	35	12.5	20	26.7	+	+	+	+

(cannula in the carotid artery) was defibrinated and then centrifuged for twenty minutes at 1,000 revolutions per minute. The supernatant serum was discarded and the remaining red cells were resuspended in isotonic saline. This suspension of red cells was then completely hemolyzed by freezing and thawing. The amount of potassium in the laked red cell suspension was then determined. This solution was then injected intravenously at the rate of 2.0 to 3.0 c.c. and 4.0 to 5.0 c.c. per minute into Rabbits 22 and 23, respectively, until the animals died (Table III, Experiments 22 and 23). Packed cell volume was determined in Experiment 23 by the method described.

To rule out the possible effects of anoxia produced by the extensive destruction of the red cells, electrocardiograms (Lead II) and serum potassium studies were performed on rabbits made anoxic, (1) by overdose with Nembutal (one rabbit), (2) by clamping of the trachea (one rabbit), and (3) by complete exsanguination of the donor rabbits when obtaining blood for the experiments described in (C).

To determine the time and dosage relationship of the action of 1 per cent saponin on rabbit's blood, the following experiments were performed in vitro. First, 9.0 c.c. of rabbit's citrated blood was placed in five graduated test tubes. Then at three-minute intervals 1.0 c.c. of 1 per cent saponin was added successively to each tube. At the end of fifteen minutes the five tubes along with a control were centrifuged for fifteen minutes at approximately 3,000 revolutions per minute. Then the packed cell volumes were determined, and the result was taken as the degree of hemolysis obtained.

In another experiment, varying amounts of saponin were added to tubes of blood each containing 9.0 c.c. of rabbit's citrated blood to make serial dilutions. These tubes of blood were allowed to stand for fifteen minutes, centrifuged for fifteen minutes at 3,000 revolutions per minute, and the degree of hemolysis determined from the remaining packed cell volumes.

RESULTS

In Vitro Experiment of 1 Per Cent Saponin and Citrated Rabbit Blood.—Laking of blood by saponin depends on its affinity for the lipoids of the cell envelope and stroma.[13] From the results of the in vitro experiments with 1 per cent saponin and citrated rabbit's blood, it is apparent that saponin acts rapidly, but only if it is present in sufficient concentration. It appears that the hemolysis obtained with smaller quantities of the 1 per cent saponin was probably due to the high concentration at the point and time of mixing. From these experiments, it would not be justifiable to assume that the amount of hemolysis obtained in any experiment was in any way proportional to the quantity of saponin given. Therefore, a quantity of 1 per cent saponin, which when given rapidly produces a marked hemolysis, may actually hemolyze a larger number of red blood cells than a greater quantity of saponin given more slowly.

The packed cell volume of citrated rabbit's blood was found to be approximately 30 to 35 per cent of the blood, as compared to 40 per cent packed cells when clotted blood was used.

Intravascular Laking by Saponin.—The experiments in which 1 per cent saponin was injected to produce intravascular hemolysis are summarized in Table 1. It can be seen that when the hemolysis was rapid and fairly extensive, higher levels of serum potassium were obtained than when the hemolysis was more gradual or less extensive. If one assumes that the decrease in packed cell volume is roughly proportional to the percentage of red cells hemolyzed, it is noted that the degree of intravascular hemolysis found necessary to raise the concentration of the serum potassium from the normal of 4 meq. to 15 meq. per liter or more, varied from 12.5 to 65 per cent of the animal's blood cells, depending mainly on the rate and degree of the hemolysis. In Experiment 5, with a reduced rate of injection of the saponin producing a more gradual and perhaps less extensive hemolysis, the serum potassium did not rise above 8.5 meq. per liter at the end of sixty minutes. However, in Experiment 21, although the degree of hemolysis was approximately the same as in Experiment 3, the rate was much faster, and a level of serum potassium of 20 meq. per liter was obtained in twenty minutes.

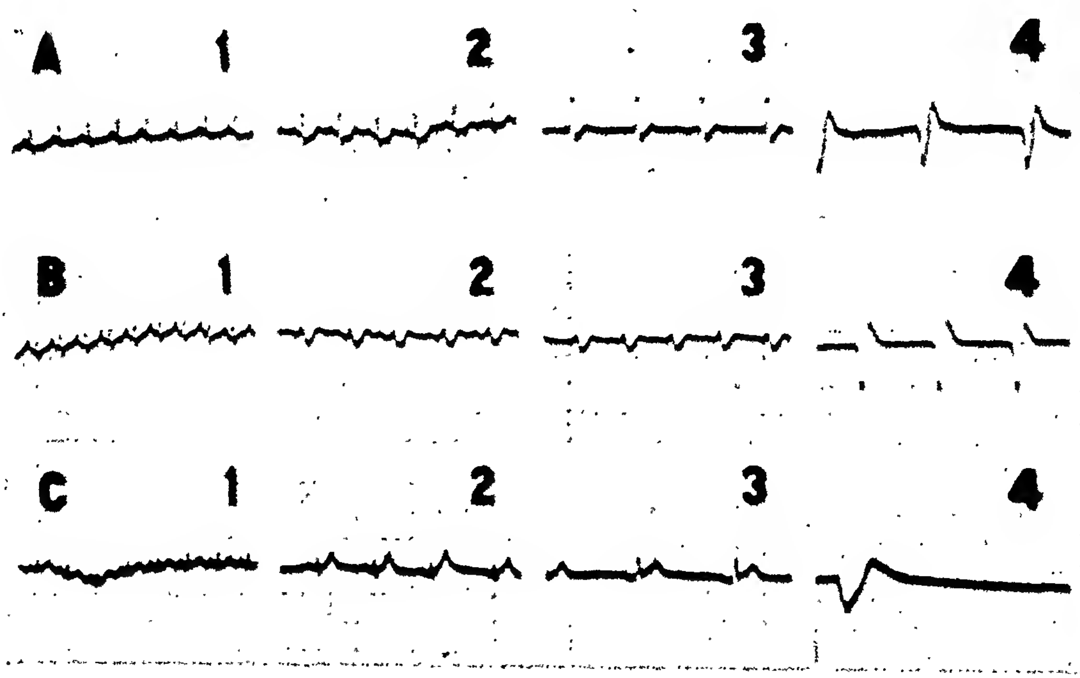

Fig. 1.—*A*, *B*, and *C* are typical of the sequence of electrocardiographic changes obtained with injection of 1.0 per cent saponin (*A*), injection of human laked blood (*B*), and rabbit's laked red cells (*C*).

A, (*1*) Control, Lead II. (*2*) Elevated T wave, RS-T segment depressed, P waves present. (*3*) P waves have disappeared, RS-T segment depressed. (*4*) Early disorganization of the QRS complex.

B, (*1*) Control, Lead II. (*2*) Slight elevation of T wave, RS-T segment depressed, P wave present. (*3*) P waves have disappeared, RS-T segment depressed. (*4*) Early disorganization of QRS complex.

C, (*1*) Control, Lead II. (*2*) Marked elevation of T wave, only slight depression of RS-T segment. (*3*) Elevated T wave, P wave flattened but still present. (*4*) Terminal disintegration of entire QRS complex.

From the data in Table I, it can be seen that the electrocardiograms obtained reflected the concentration of the serum potassium. In Experiments 3 and 17, at concentrations of potassium between 5.9 and 8.5 meq. per liter, the electrocardiographic changes were limited to elevated or biphasic T waves, and RS-T segment depression (see Fig. 1,*A*). The loss of the P wave was noted at a concentration of 8.9 meq. per liter and higher. In Experiments 7, 13, and 21, at serum potassium levels of between 11.7 and 14.5 meq. per liter, the electrocardiograms showed elevation of the T wave, RS-T segment depression, loss of the P wave, and beginning widening of the QRS complex, but complete disintegration of the QRS complex was not yet apparent. Complete disintegration of the QRS complex and final cardiac arrest were observed only when the serum potassium levels were 14.9 meq. per liter and over, the average level being approximately 16.8 meq. per liter. The levels of serum potassium and the associated electrocardiographic changes noted in these experiments are very similar to those reported following the slow injection of isotonic potassium chloride in dogs[3] and in rabbits.[6]

Ventricular extrasystoles, ventricular tachycardia, and bigeminal rhythms were seen frequently in some experiments, and these were probably due to a toxic action of saponin. In Experiment 18, where the rate of hemolysis was very rapid, spontaneous ventricular fibrillation occurred four minutes from the start of the saponin injection, and the serum potassium at that instant was 13.3 mEq per liter. In Experiments 3, 17, and 20, ventricular fibrillation was precipitated by the insertion of the hypodermic needle into the heart for the withdrawal of blood for potassium determination. In Experiments 7 and 13, where no intratracheal oxygen was given, respiration ceased and the experiments were terminated before sufficient hemolysis had occurred to produce lethal levels of serum potassium.

Intravenous Injection of Human Blood.—The data of the experiments with citrated whole human blood (Group O) and with laked human blood are presented in Table II.

All the animals died of cardiac arrest within twenty-four minutes from the onset of the injection. Death in each case was preceded by the typical sequence of electrocardiographic changes as in the case of the saponin experiments (Fig. 1,*B*). Very high concentrations of serum potassium were found terminally in these experiments. The extremely high levels were due to the fact that there was a sudden partial to complete intravascular hemolysis of the rabbit's own cells as well as that of the donor cells (human).

Intravenous Injection of Laked Rabbit Cells.—In Table III are summarized the data in the experiment with the laked rabbit red cells. The potassium concentration in the laked red cell suspension was 32.0 mEq per liter.

Here again, terminally, the rabbits showed lethal levels of serum potassium with death by cardiac arrest. The electrocardiographic changes were again characteristic of potassium intoxication (Fig. 1,*C*). Although the total amount of laked red cells injected into Rabbits 22 and 23 was approximately the same, the faster rate of injection in Experiment 23 resulted in a higher level of serum potassium in a shorter time.

Control Studies.—In the rabbit made anoxic with excess Nembutal, as well as in the rabbit with the trachea clamped, electrocardiograms revealed some elevation of the T wave and RS-T segment depression. The complexes decreased in amplitude and varying degrees of heart block were noted terminally. In no instance was there a loss of the P wave or a broadening or disintegration of the QRS complex characteristic of potassium intoxication. The serum potassium determined terminally for the rabbit with the trachea clamped was 5.6 meq. per liter. In a series of electrocardiograms taken on four rabbits which were completely exsanguinated, the changes consisted of T-wave elevation, depression of the RS-T segment, and only in one instance was there a loss of the P wave, but the animal did not show disintegration of the QRS complex noted in the experiments with saponin and laked red cells. Terminally, these animals showed varying degrees of heart block. The serum potassium in one of the exsanguinated rabbits was terminally increased to 7.4 meq. per liter.

DISCUSSION

These experiments demonstrate that sudden intravascular hemolysis may liberate sufficient potassium to cause cardiac arrest. In all experiments, the correlation between the sequence of electrocardiographic changes and the concentrations of serum potassium resembled very closely that found in animals given slow intravenous injections of isotonic potassium chloride[3,6] (Fig. 1 *A*, *B*, and *C*).

Although there was no direct relation between the amount of saponin injected and the extent of hemolysis found, it has been noted that in those experiments where the saponin was given more quickly, the rate and degree of hemolysis was greater, and higher levels of serum potassium with corresponding electrocardiographic changes occurred sooner than when the saponin was given more slowly (Table I). This may be due partly to the fact that when the hemolysis was more gradual, the excess serum potassium had more time to diffuse into the remaining extracellular fluid or be excreted by the kidneys, and the serum potassium never reached such high levels. It would appear, therefore, that the rate and degree of intravascular hemolysis are the important factors in determining the level of serum potassium obtained.

Since the packed cell volume determinations were made on partially clotted blood, it is evident that the values for the amount of hemolysis obtained were probably less than the actual degree of hemolysis present in each case. However, it is significant that the range of hemolysis in these experiments is in close accord with the calculated range necessary to elevate the serum potassium to 15 meq. per liter.

Because of the relatively short duration of each experiment, the ligation of the ureters in Rabbits 2, 3, 5, and 8 did not significantly affect the final outcome of these experiments.

The ventricular extrasystoles, ventricular tachycardia, and the begiminal rhythm, noted only in the saponin experiments, were probably due to saponin, a plant glucoside; but the spontaneous ventricular fibrillation noted in Experiment 18 was probably precipitated by the sudden elevation of the serum potas-

sium to 13.4 meq. per liter. Similar observations were made when isotonic chloride was rapidly injected into rabbits.[6]

Saponin can cause paralysis of the respiratory center,[13] as was noted in some of our experiments, but the use of continuous intratracheal oxygen tended to prevent anoxia. The observation had been previously made by Gottdenker[12] that in rabbits, doses of saponin of 20 mg. per kilogram of body weight resulted in death associated with extreme degrees of cardiac dilatation. However, applied to isolated strips of auricular muscle, saponin caused arrhythmias and ultimately death in contraction. It thus seems likely that the cardiac dilatation observed by Gottdenker was probably due to the terminal cardiac arrest in diastole caused by the excess serum potassium from the intravascular hemolysis.

Terminal serum potassium levels in the anoxic control rabbits were only slightly elevated, and electrocardiograms did not show the sequence of changes seen in potassium intoxication. These small elevations of serum potassium are in accord with the observations of Mullen, Dennis, and Calvin,[14] who found an increase of serum potassium up to 30 per cent of the original value in anoxic dogs. Scudder[15] also found similar small increases in serum potassium in cases of shock due to hemorrhage. Therefore, it may safely be assumed that any degree of anoxia present in these experiments did not raise the serum potassium sufficiently to account for the high levels of potassium and the associated electrocardiographic changes obtained.

The mechanism of death in cases of acute intravascular hemolysis is still not fully understood. The results of these experiments suggest that the sudden and extensive hemolysis seen in some cases of incompatible transfusion reaction, in erythroblastosis fetalis, and in cases of acute intravascular hemolysis from other causes can cause death from potassium intoxication. It is also obvious that impairment of renal function sufficient to prevent excretion of excess potassium will increase the possibility of lethal levels of serum potassium being reached.[16]

CONCLUSIONS

1. It has been shown that in rabbits, rapid intravascular hemolysis of red cells, by liberation of the intracellular potassium into the plasma, can cause death by potassium intoxication.

2. The possible implication of this in clinical cases of intravascular hemolysis has been discussed.

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AN ANALYSIS OF THE RELATIVE ACCURACIES OF THE WILSON AND GOLDBERGER METHODS FOR REGISTERING UNIPOLAR AND AUGMENTED UNIPOLAR ELECTROCARDIOGRAPHIC LEADS

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INTRODUCTION

A UNIPOLAR electrocardiographic lead is a graphic representation of the cardiac action potentials which are present at one particular location on a subject's body with respect to a nonfluctuating reference. It is differentiated from the usual bipolar electrocardiographic lead, for example, Lead I, in which the action potentials of the right and left arms fluctuate and the resultant electrocardiogram is an algebraic addition of these potentials with respect to time.

In 1932 Wilson, Johnston, Macleod, and Barker[1,2] suggested that a central terminal or nonfluctuating reference for unipolar leads may be obtained by connecting the right arm, left arm, and left leg to a junction point via three equal resistances. They suggested that the accuracy of the method is dependent upon the validity of the equilateral triangle of Einthoven, Fahr, and De Waart[3] and Kirchhoff's[4] laws of electric networks.

Kirchhoff's two laws pertaining to electric networks were first formulated in 1845. They are special expressions of relations explicit in field equations applicable to electric circuits. The first law, known as the voltage law, states: *If in an electric network a closed path is traversed, the algebraic sum of voltages across the individual elements in the direction of traversal is zero.* The second law, known as the current law, states: *The algebraic sum of all currents directed toward and away from a junction is zero* because electricity behaves like an incompressible fluid. By means of Kirchhoff's laws it is possible to determine the resultant behavior of any lumped-parameter linear electric network such as a unipolar electrocardiographic lead.

Wilson, Johnston, Macleod, and Barker observed that according to Kirchhoff's second law the potential of the junction or central terminal must be equal at every instant to the mean of the potentials of the electrodes on the right arm, left arm, and left leg. If the assumption is now made that the equilateral triangle of Einthoven, Fahr, and De Waart is valid and that the electrical forces of cardiac origin which are perpendicular to the plane formed by the limb leads

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have negligible effect upon the variations in potential at the limbs, then the central terminal cannot be materially affected by the action potentials throughout the cardiac cycle.

The validity of Kirchhoff's laws as applied to central terminal calculation is unquestionable. They are universally employed and accepted as an important tool by the mathematical physicist and electrical engineer for the calculation of electric networks. The application of Kirchhoff's laws to the central terminal circuit is comparatively simple and straightforward. On the other hand, there has been controversial discussion[5,6] as to the validity of the equilateral triangle of Einthoven, Fahr, and De Waart. Unfortunately, it is most difficult to prove the validity of the equilateral triangle by mathematical means because of the extremely complex nature of the electrical field produced by the heart beat. As a result, experimental methods have been employed by a number of investigators.[7,8,9,10] The general procedure employed by Fahr and Weber,[7] Wagner,[8] and Johnston, Kossmann, and Wilson[9] was to apply constant or variable potentials via two metallic electrodes inserted in the heart of a cadaver and to compute from the differences in potential in the limb leads whether the relationships expressed in the equilateral triangle of Einthoven, Fahr, and De Waart hold true. Wilson and Herrmann[10] stimulated the heart of a living dog by means of an inductorium connected to two electrodes in the ventral wall of the heart, one near the base and the other near the apex. The electrodes were so located that a line joining them was very nearly parallel to the long axis of the body. *All of the investigators found that the direction and relative magnitude of the deflections in the limb leads were comparable, within close limits, with the relationships expressed in the equilateral triangle theory.*

Burger and Whurmann[11] compared the central terminal of the Einthoven, Fahr, and De Waart triangle with that of other central terminals, each connected to a set of three electrodes located equidistant from the heart and lying at the apices of a triangle enclosing it. They observed that the potential differences between the various central terminals were practically zero. Wilson and his co-workers[12] carried out similar experiments. They state: "Arrighi is known to have carried out experiments of a similar kind. So far as we know, his work has not yet been published, but all of his experiments that we have knowledge of yielded results comparable to those reported by Burger and Wuhrmann. We have performed one experiment of the same kind and the results of such experiments are predictable on the basis of Arrighi's[13] published work." Wilson and associates[12] employed the Arrighi triangle and compared its potential with that of the equilateral triangle of Einthoven, Fahr, and De Waart and found that the difference in potential did not exceed 0.15 millivolt. The Arrighi triangle is obtained as follows: one electrode is placed in the left submaxillary region close to the chin, the second 3.0 or 4.0 cm. to the left of the midpoint of a line joining the umbilicus with the center of the pubis, and a third in the left interscapular space, approximately at the level of the spinous process of the seventh thoracic vertebra.

A possible source of error in the application of the Einthoven triangle hypothesis to unipolar electrocardiography lies in the position of the frontal

plane determined by the three reference points (right arm, left arm, and left leg). Some doubt has been expressed as to the inclusion of the center of electrical activity of the heart in the frontal plane. If this plane does not pass through the center of electrical activity, the potential of the central terminal will be positive or negative, depending upon the spatial relationship of the heart to the plane in an electrical sense.

Eckey and Fröhlich,[15] Burger,[16] and Wilson and associates[12] have performed immersion experiments to ascertain the degree of potential fluctuation that may occur between the central terminal formed by the Einthoven equilateral triangle and the central terminal by immersion. Eckey and Fröhlich employed distilled water and completely immersed the subject in a metal-lined tub; the subject was allowed to breathe through a tube. The electrodes employed for obtaining the central terminal formed by the right arm, left arm, and left leg were not insulated from the distilled water; the immersion central terminal was the metal lining of the tub. Eckey and Fröhlich observed a slight modification in the limb lead deflections after immersion due to the slight electrical conductivity of the distilled water. The greatest variations in potential observed between the two central terminals in an unspecified number of experiments was of the order 0.3 millivolt. Burger employed a zinc tub filled with tap water, but the subject's face was not immersed and the limb electrodes were insulated from the water. Burger observed a 25 per cent reduction in the standard limb lead deflections which may be ascribed to the conductivity of tap water. In five normal subjects the greatest potential difference between the two central terminals was approximately 0.26 millivolt. Wilson and associates immersed the subject up to the neck in a fresh-water lake. The immersion central terminal was a large metal electrode suspended in the lake approximately eleven feet from the body. The short-circuiting effect of the lake water reduced the standard limb lead deflections approximately 50 per cent. The largest potential variation measured between the two central terminals was 0.15 millivolt. These authors did not state whether the limb electrodes were insulated from the water. They concede that a certain degree of error is present in the immersion experiments but conclude that the central terminal formed by the right arm, left arm, and left leg is a good approximation of a nonfluctuating reference.

In 1942 Goldberger[14] suggested that unipolar electrocardiographic leads may be obtained by means of the Wilson technique, with the exception that the central terminal be formed by connecting the right arm, left arm, and left leg directly to a junction point without interposing the 5,000 ohm resistors. In other words, the Goldberger method depends entirely upon the subject resistance in each limb. Wilson and his co-workers[1,2] at first thought that 25,000 ohm resistors in each limb circuit would produce a central terminal more nearly unipotential. They decided, however, to use 5,000 ohms because of the greater susceptibility of the electrocardiographic apparatus to alternating current interference when 25,000 ohm resistors are employed. *The purpose of the resistors in each limb circuit is to minimize differences in subject resistance at each limb. Theoretically, dissimilarity in contact resistance of each limb introduces variation in*

current distribution in the central terminal circuit which affects the potential of the central terminal.

The Goldberger modification is widely employed in clinical electrocardiography. In this paper it is our object to show mathematically the relative accuracies of the Wilson and Goldberger methods. An actual comparison of unipolar electrocardiograms taken with Wilson and Goldberger leads was made by Bryant and Johnston[19,20] in a series of 500 cases, using only the left leg lead (aV_F). A significant difference between the Wilson and Goldberger techniques was observed in 10 per cent of the cases.

We are in the process of a more extensive investigation in which a comparison of the electrocardiograms taken with both techniques is being made. In addition, the actual measurement of the resistances as they exist at the points of contact of electrodes to the limbs is being made. These results will be published in subsequent papers.

THE CENTRAL TERMINAL

The basic circuit of a central terminal in which the resistances in the three limb circuits are equal is shown in Fig. 1. This condition occurs in the Wilson method when the patient resistances of each limb are identical and each is in series with a 5,000 ohm resistor. That is, R is equal to limb resistance plus 5,000 ohms. When the Goldberger method is employed, the condition of Fig. 1 occurs when the patient resistances of the limbs are equal. That is, R is equal to the resistance of each limb. Let

e_0 = voltage at the central terminal as a result of cardiac action
e_1 = instantaneous voltage at the right arm electrode as a result of cardiac action
e_2 = instantaneous voltage at the left arm electrode as a result of cardiac action
e_3 = instantaneous voltage at the left leg electrode as a result of cardiac action
E_1 = instantaneous voltage between the right arm electrode and the central terminal
i_1 = current flow between right arm electrode and central terminal
i_2 = current flow between left arm electrode and central terminal
i_3 = current flow between left leg electrode and central terminal

The arrows associated with current flow are arbitrarily assumed according to Kirchhoff's second law. According to Ohm's law, which states that the current in a conducting system at any instant is equal to the applied voltage divided by the resistance offered to the flow of current, we may state that in Fig. 1

$$i_1 = \frac{e_1 - e_0}{R} \qquad [1]$$

$$i_2 = \frac{e_2 - e_o}{R} \quad [2]$$

$$i_3 = \frac{e_o - e_3}{R} \quad [3]$$

From the indicated direction of current flow in Fig. 1,

$$i_3 = i_1 + i_2 \quad [4]$$

Substituting Equations 1, 2, and 3 in Equation 4

$$\frac{e_o - e_3}{R} = \frac{e_1 - e_o}{R} + \frac{e_2 - e_o}{R}$$

$$\therefore \quad 3\,e_o = e_1 + e_2 + e_3$$

or $$e_o = \frac{e_1 + e_2 + e_3}{3} \quad [5]$$

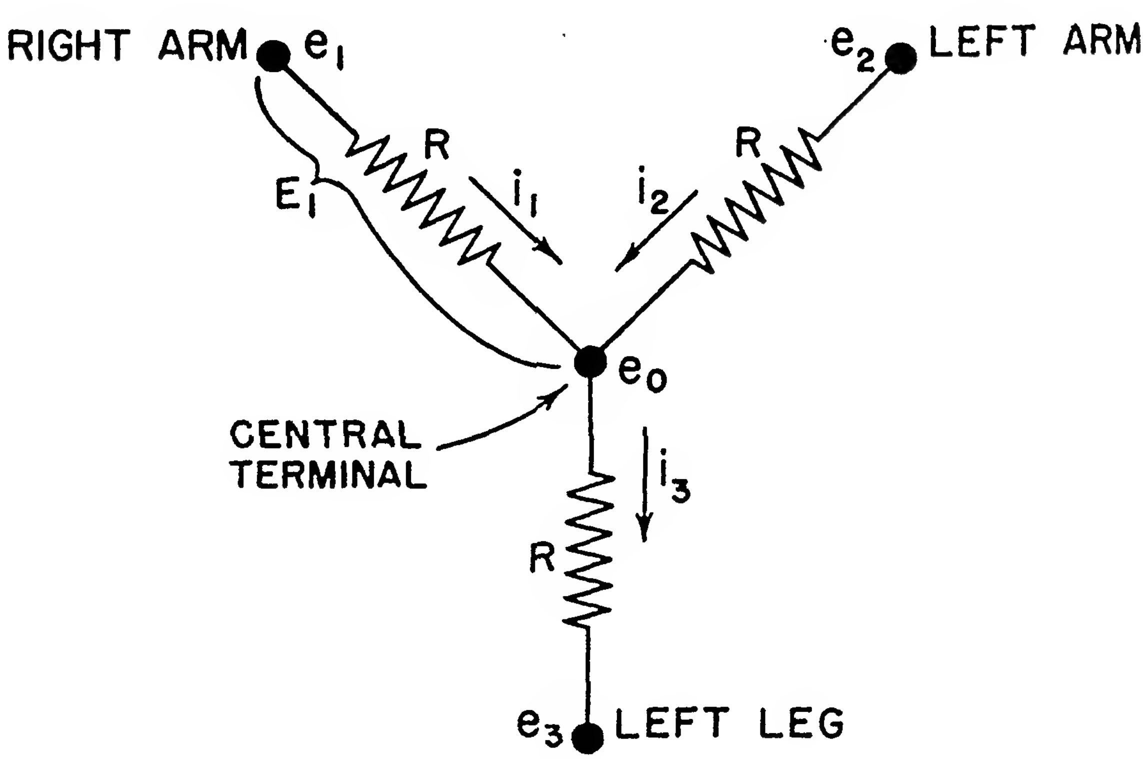

Fig. 1.—The basic circuit of a central terminal in which the resistances in the three limb circuits are equal.

Equation 5 is the Wilson, Macleod, and Barker formula which states that the potential of the central terminal must be equal at every instant to the mean of the potentials of the electrodes on the right arm, left arm, and left leg. Also

$$E_1 = e_1 - e_o \qquad [6]$$

By substituting Equation 5 into Equation 6, we get

$$E_1 = e_1 - \left[\frac{c_1 + e_2 + e_3}{3}\right]$$

or

$$E_1 = e_1 - \frac{e_1}{3} - \frac{e_2}{3} - \frac{e_3}{3} \qquad [7]$$

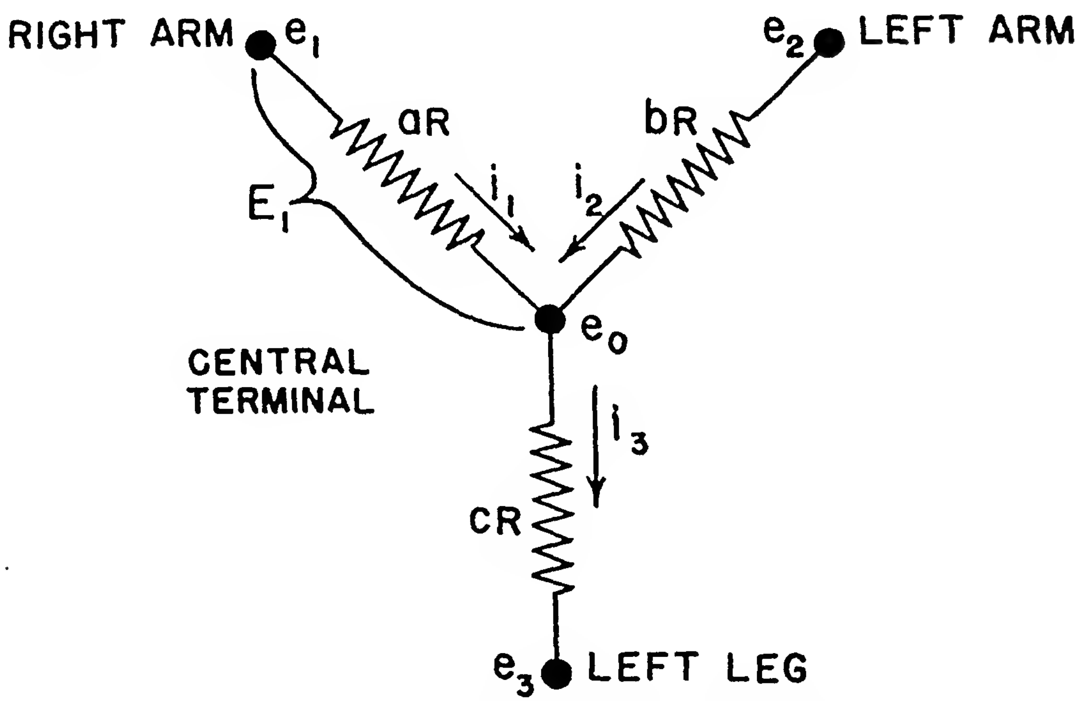

Fig. 2.—The basic circuit of a central terminal in which the resistances in the three limb circuits are dissimilar because of differences in the resistance of the right arm, left arm, and left leg.

Let us now consider the Wilson circuit in Fig. 2 where unlike values of patient resistance are present in each limb circuit. If we let

a, b, and c = factors which, when multiplied by the nominal limb circuit resistance R, give the actual limb circuit resistance,

then

$$i_1 = \frac{e_1 - e_o}{aR} \qquad [8]$$

$$i_2 = \frac{e_2 - e_o}{bR} \qquad [9]$$

$$i_3 = \frac{e_o - e_3}{cR} \qquad [10]$$

also $$i_3 = i_1 + i_2 \qquad [11]$$

By substituting Equations 8, 9, and 10 in Equation 11 we get

$$\frac{e_o - e_3}{cR} = \frac{e_1 - e_o}{aR} + \frac{e_2 - e_o}{bR}$$

$$\therefore \quad \frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c} = \frac{e_o}{a} + \frac{e_o}{b} + \frac{e_o}{c}$$

$$\frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c} = e_o \left[\frac{1}{a} + \frac{1}{b} + \frac{1}{c}\right]$$

$$\frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c} = e_o \left[\frac{bc + ac + ab}{abc}\right]$$

or $$e_o = \left[\frac{e_1}{a} + \frac{e_2}{b} + \frac{e_3}{c}\right]\left[\frac{abc}{bc + ac + ab}\right]$$

$$\therefore \quad e_o = \frac{bce_1 + ace_2 + abe_3}{bc + ac + ab} \qquad [12]$$

A reasonable assumption is that the following values of patient resistance may exist in a hypothetical case

right arm = *1,000 ohms*
left arm = *2,000 ohms*
left leg = *3,000 ohms*

Therefore,

$a = 1/2$
$b = 1$
$c = 3/2$

If we substitute these values of patient resistance in Equation 12 we get

$$e_o = \frac{\frac{3}{2} e_1 + \frac{3}{4} e_2 + \frac{1}{2} e_3}{\frac{3}{2} + \frac{3}{4} + \frac{1}{2}} = \frac{\frac{3}{2} e_1 + \frac{3}{4} e_2 + \frac{1}{2} e_3}{\frac{11}{4}} \qquad [13]$$

If we now take a case where the instantaneous voltages at the three limb electrodes are

$$\begin{aligned} \textit{right arm} &= e_1 = -1.2 \textit{ mv.} \\ \textit{left arm} &= e_2 = +0.9 \textit{ mv.} \\ \textit{left leg} &= e_3 = +0.3 \textit{ mv.} \end{aligned}$$

According to Equation 5, the theoretically correct voltage at the central terminal as a result of cardiac action is

$$\underset{\text{[Theoretical]}}{e_o} = \frac{e_1 + e_2 + e_3}{3} = \frac{-1.2 + 0.9 + 0.3}{3} = 0 \textit{ mv.}$$

which is the mean value of the potentials at the three limbs.

According to equation 13

$$\underset{\text{[Goldberger]}}{e_o} = \frac{-\frac{3}{2} \times 1.2 + \frac{3}{4} \times 0.9 + \frac{1}{2} \times 0.3}{\frac{11}{4}} = -0.355 \textit{ mv.}$$

In the Wilson central terminal the resistance in the

$$\begin{aligned} \textit{right arm circuit} &= 1{,}000 + 5{,}000 = 6{,}000 \textit{ ohms} \\ \textit{left arm circuit} &= 2{,}000 + 5{,}000 = 7{,}000 \textit{ ohms} \\ \textit{left leg circuit} &= 3{,}000 + 5{,}000 = 8{,}000 \textit{ ohms} \end{aligned}$$

Thus,

$$a = 6/7$$
$$b = 1$$
$$c = 8/7$$

If we substitute these values into Equation 12 we get

$$\underset{\text{[Wilson at 5,000 ohms]}}{e_o} = \frac{-1 \times \frac{8}{7} \times 1.2 + \frac{6}{7} \times \frac{8}{7} \times 0.9 + \frac{6}{7} \times 1 \times 0.3}{1 \times \frac{8}{7} + \frac{6}{7} \times \frac{8}{7} + \frac{6}{7} \times 1} = -0.077 \textit{ mv.}$$

When 10,000 ohm resistors are employed in the Wilson central terminal instead of 5,000 ohms, then

$$\begin{aligned} \textit{right arm circuit} &= 1{,}000 + 10{,}000 = 11{,}000 \textit{ ohms} \\ \textit{left arm circuit} &= 2{,}000 + 10{,}000 = 12{,}000 \textit{ ohms} \\ \textit{left leg circuit} &= 3{,}000 + 10{,}000 = 13{,}000 \textit{ ohms} \end{aligned}$$

Therefore,

$$a = 11/12$$
$$b = 1$$
$$c = 13/12$$

If we substitute these values in Equation 12, we get

$$e_o \text{ [Wilson at 10,000 ohms]} = \frac{-1 \times \frac{13}{12} \times 1.2 + \frac{11}{12} \times \frac{13}{12} \times 0.9 + \frac{11}{12} \times 1 \times 0.3}{1 \times \frac{13}{12} + \frac{11}{12} \times \frac{13}{12} + \frac{11}{12} \times 1} = -0.043 \text{ mv.}$$

Our calculations show, therefore,

Theoretically correct voltage at central terminal = 0 mv.
Wilson central terminal voltage employing 10,000 ohm resistors = −0.043 mv.
Wilson central terminal voltage employing 5,000 ohm resistors = −0.077 mv.
Goldberger central terminal voltage = −0.355 mv.

E_1 is the instantaneous voltage between the right arm and the central terminal or what is clinically termed as the V_R or right unipolar limb lead. The effect on this lead by the unbalance due to unequal patient resistance in the right arm, left arm, and left leg may be calculated in the following manner:

$$E_1 \text{ [Theoretical]} = e_1 - e_o = -1.2 + 0 = -1.2 \text{ mv.}$$

$$E_1 \text{ [Wilson at 10,000 ohms]} = -1.2 + 0.043 = -1.157 \text{ mv.}$$

$$E_1 \text{ [Wilson at 5,000 ohms]} = -1.2 + 0.077 = -1.123 \text{ mv.}$$

$$E_1 \text{ [Goldberger]} = -1.2 + 0.355 = -0.845 \text{ mv.}$$

The voltage errors introduced in the V_R lead by the Wilson and Goldberger methods are:

Wilson central terminal with 10,000 ohm resistors = 3.59 per cent error
Wilson central terminal with 5,000 ohm resistors = 6.42 per cent error
Goldberger central terminal = 29.5 per cent error

THE AUGMENTED UNIPOLAR EXTREMITY LEADS

Unipolar extremity leads as taken with the original Wilson technique are usually of rather low magnitude. To facilitate a reasonable degree of accuracy in the reading of the graph, it is usually desirable to increase the sensitivity of the

electrocardiograph to 1.5 or 2 cm. per millivolt. *Goldberger*[14] *suggested that all complexes in unipolar extremity leads are increased by a factor of 1.5 if the connection from the central terminal is removed from the limb under investigation.* Goldberger suggested that the extremity lead which is registered with an increased magnitude of 1.5 times normal be called the *augmented unipolar extremity lead* and be symbolized as follows:

aV_R = augmented unipolar right arm
aV_L = augmented unipolar left arm
aV_F = augmented unipolar left leg

Let us now determine by mathematical calculation the accuracy of Goldberger's relationship. Fig. 3 is a representation of the basic electrical circuit which is created when an augmented unipolar right arm lead is taken as suggested by Goldberger. Let us also assume an ideal condition in which the patient resistances in the left arm and left leg are equal. Then

e'_o = voltage at the central terminal as a result of cardiac action
E'_1 = instantaneous potential difference between right arm and central terminal which is the aV_R lead
E_1 = instantaneous potential difference between right arm and central terminal representing the unipolar right extremity (V_R) lead of Fig. 2
e_1 = instantaneous potential at right arm electrode as a result of cardiac action
e_2 = instantaneous potential at left arm electrode as a result of cardiac action
e_3 = instantaneous potential at left leg electrode as a result of cardiac action

From Fig. 3 it is obvious that

$$e'_o = \frac{e_2 + e_3}{2} \qquad [14]$$

also $$E'_1 = e_1 - e'_o \qquad [15]$$

If we substitute Equation 14 into Equation 15, we get

$$E'_1 = e_1 - \left[\frac{e_2 + e_3}{2}\right] = e_1 - \frac{e_2}{2} - \frac{e_3}{2} \qquad [16]$$

But $$E'_1 - E_1 = aV_R\ lead - V_R\ lead \qquad [17]$$

Using Equations 16 and 7, we may say that

$$E'_1 - E_1 = e_1 - \frac{e_2}{2} - \frac{e_3}{2} - e_1 + \frac{e_1}{3} + \frac{e_2}{3} + \frac{e_3}{3}$$

$$E'_1 - E_1 = \frac{e_1}{3} - \frac{e_2}{6} - \frac{e_3}{6} = \frac{1}{3}\left[e_1 - \frac{e_2}{2} - \frac{e_3}{2}\right]$$

or $$E'_1 - E_1 = \frac{1}{3} E'_1$$

$$\therefore \quad E'_1 = \frac{3}{2} E_1 = 1.5\ E_1 \qquad [18]$$

The derivation of Equation 18 is a mathematical proof which substantiates Goldberger's relationship that the aV_R lead is identical in configuration to the V_R lead but increased by a factor of 1.5 when the patient resistances in the left arm and left leg are identical.

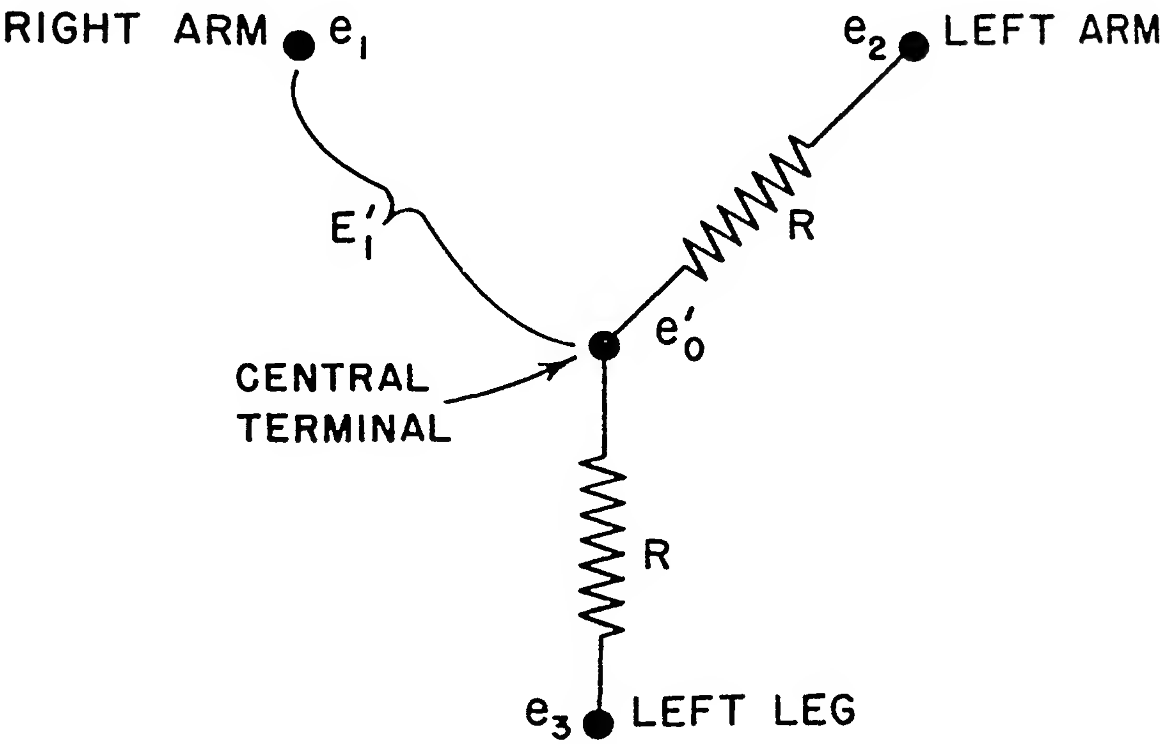

Fig. 3.—The basic circuit of an augmented unipolar right arm lead in which the patient resistances in the left arm and left leg circuits are equal.

From Fig. 3 and the preceding calculation on the augmented unipolar extremity leads it is obvious that the Wilson central terminal may be used exactly like the Goldberger central terminal to obtain the aV_R, aV_L, and aV_F leads. The basis for this assumption is that *R* in Fig. 3 is merely the sum of limb resistance plus the value of the resistor in the Wilson central terminal circuit and the mathematical derivation is thus unaffected.

Let us now consider the effects of dissimilar patient resistance in the extremities. In the calculations that are to follow we may assume that in Fig. 4

e_1 = instantaneous potential at right arm electrode as a result of cardiac action
e_2 = instantaneous potential at left arm electrode as a result of cardiac action
e_3 = instantaneous potential at left leg electrode as a result of cardiac action
e''_o = voltage at the central terminal as a result of cardiac action
E''_1 = instantaneous potential difference between right arm and central terminal which is the aV_R lead
bR = resistance of left arm circuit
cR = resistance of left leg circuit
i = current flow as a result of cardiac action

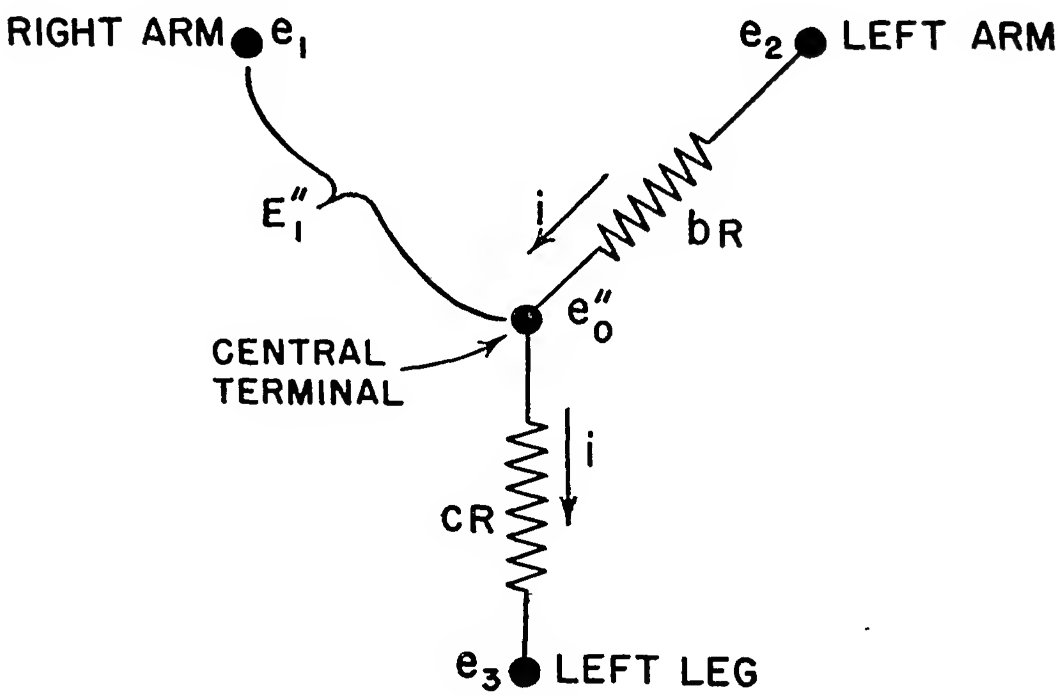

Fig. 4.—The basic circuits of an augmented unipolar right arm lead in which the patient resistances in the left arm and left leg circuits are not alike.

According to Ohm's law

$$i = \frac{e_2 - e''_o}{bR} = \frac{e''_o - e_3}{cR} \qquad [19]$$

cancelling out R we get

$$\frac{e_2 - e''_o}{b} = \frac{e''_o - e_3}{c}$$

$$\frac{e_2}{b} - \frac{e''_o}{b} = \frac{e''_o}{c} - \frac{e_3}{c}$$

$$\frac{e_2}{b} + \frac{e_3}{c} = \frac{e''_o}{c} + \frac{e''_o}{b} = e''_o \left[\frac{1}{c} + \frac{1}{b}\right]$$

or

$$e''_o = \frac{\dfrac{e_2}{b} + \dfrac{e_3}{c}}{\dfrac{1}{c} + \dfrac{1}{b}} = \frac{e_2\, c + e_3\, b}{b + c} \qquad [20]$$

As previously, let patient resistance in

left arm = *2,000 ohms*
left leg = *3,000 ohms*

Also as before, let

$e_2 = 0.9$ *mv.*
$e_3 = 0.3$ *mv.*

According to Equation 14, the theoretically correct augmented central terminal voltage is

$$e''_o\ \text{[Theoretical]} = \frac{e_2 + e_3}{2} = \frac{0.9 + 0.3}{2} = 0.6 \text{ mv.}$$

If the Wilson central terminal composed of 10,000 ohm resistors is used to obtain the augmented unipolar limb lead, the resistance of

left arm = *2,000 + 10,000 = 12,000 ohms*
left leg = *3,000 + 10,000 = 13,000 ohms*

Thus,

$b = 1$
$c = 13/12$

According to Equation 20, the augmented central terminal voltage by the Wilson technique with 10,000 ohm resistors is

$$e''_o\ \text{[Wilson at 10,000 ohms]} = \frac{c_2\, c + e_3\, b}{b + c} = \frac{0.9 \times \dfrac{13}{12} + 0.3 \times 1}{1 + \dfrac{13}{12}} = 0.612 \text{ mv.}$$

When the Wilson technique with 5,000 ohm resistors is used,

left arm = *2,000 + 5,000 = 7,000 ohms*
left leg = *3,000 + 5,000 = 8,000 ohms*

Thus,

$b = 1$
$c = 8/7$

$$\text{or} \quad e''_{o\,[\text{Wilson at 5,000 ohms}]} = \frac{0.9 \times \frac{8}{7} + 0.3 \times 1}{1 + \frac{8}{7}} = 0.62 \text{ mv.}$$

If the Goldberger technique is used

left arm = *2,000 ohms*
left leg = *3,000 ohms*

Thus,

$b = 1$
$c = 3/2$

$$\text{or} \quad e''_{o\,[\text{Goldberger}]} = \frac{0.9 \times \frac{3}{2} + 0.3 \times 1}{1 + \frac{3}{2}} = 0.66 \text{ mv.}$$

Our calculations therefore show:

Theoretically correct voltage at central terminal = 0.6 mv.
Wilson central terminal voltage employing 10,000 ohm resistors = 0.612 mv.
Wilson central terminal voltage employing 5,000 ohm resistors = 0.62 mv.
Goldberger central terminal voltage = 0.66 mv.

E'' is the instantaneous potential difference between the right arm and the central terminal which is the aV_R lead or augmented unipolar right limb lead. The effect on this lead by patient resistance unbalance in the left arm and left leg circuits may be calculated in the following manner:

E''_1 [Theoretical] $= e_1 - e''_o = -1.2 - 0.6 = -1.8$ *mv.*
E''_1 [Wilson at 10,000 ohms] $= -1.2 - 0.612 = -1.812$ *mv.*
E''_1 [Wilson at 5,000 ohms] $= -1.2 - 0.62 = -1.82$ *mv.*
E''_1 [Goldberger] $= -1.2 - 0.66 = -1.86$ *mv.*

The voltage error introduced in the aV_R lead by the Wilson and Goldberger methods is:

Wilson method with 10,000 ohm resistors = 0.67 per cent error
Wilson method with 5,000 ohm resistors = 1.1 per cent error
Goldberger method = 3.3 per cent error

It so happens, that in this case the patient resistance discrepancy between the left arm and left leg is not as great as occurs between the right arm and left leg. If the aV_L lead were taken in this hypothetical case, the patient resistance factor should be of greater consequence. For comparative purposes, however, we may calculate the error in the aV_R lead if the left arm patient resistance is 1,000 ohms instead of 2,000 ohms. Thus,

$$\textit{left arm} = 1{,}000 \textit{ ohms}$$
$$\textit{left leg} = 3{,}000 \textit{ ohms.}$$

As before,

$$e_2 = 0.9 \textit{ mv.}$$
$$e_3 = 0.3 \textit{ mv.}$$

According to Equation 14, the theoretically correct augmented central terminal still is

$$e''_o \text{ [Theoretical]} = \frac{e_2 + e_3}{2} = \frac{0.9 + 0.3}{2} = 0.6 \textit{ mv.}$$

If the Wilson central terminal composed of 10,000 ohm resistors is used to obtain Lead aV_R, the resistance of

$$\textit{left arm circuit} = 1{,}000 + 10{,}000 = 11{,}000 \textit{ ohms}$$
$$\textit{left leg circuit} = 3{,}000 + 10{,}000 = 13{,}000 \textit{ ohms}$$

Thus,

$$b = 1$$
$$c = 13/11$$

According to Equation 20, the augmented central terminal voltage by the Wilson technique with 10,000 ohm resistors is

$$e''_o \text{ [Wilson at 10,000 ohms]} = \frac{0.9 \times \frac{13}{11} + 0.3 \times 1}{1 + \frac{13}{11}} = 0.623 \textit{ mv.}$$

When the Wilson technique with 5,000 ohm resistors is used,

$$\textit{left arm circuit} = 1{,}000 + 5{,}000 = 6{,}000 \textit{ ohms}$$
$$\textit{left leg circuit} = 3{,}000 + 5{,}000 = 8{,}000 \textit{ ohms}$$

Thus,

$$b = 1$$
$$c = 8/6$$

or

$$e''_{o\,[\text{Wilson at 5,000 ohms}]} = \frac{0.9 \times \frac{8}{6} + 0.3 \times 1}{1 + \frac{8}{6}} = 0.644 \text{ mv.}$$

When the Goldberger technique is used

left arm circuit = *1,000 ohms*
left leg circuit = *3,000 ohms*

Thus,

$b = 1$
$c = 3$

or

$$e''_{o\,[\text{Goldberger}]} = \frac{0.9 \times 3 + 0.3 \times 1}{1 + 3} = 0.75 \text{ mv.}$$

Our calculations therefore show:

Theoretically correct voltage at central terminal = 0.6 mv.
Wilson central terminal voltage employing 10,000 ohm resistors = 0.623 mv.
Wilson central terminal voltage employing 5,000 ohm resistors = 0.644 mv.
Goldberger central terminal voltage = 0.75 mv.

E'' is the instantaneous potential difference between the right arm and the central terminal which is the aV_R lead. The effect on this lead by patient resistance unbalance in the left arm and left leg circuits is:

E''_1 [Theoretical] $= e_1 - e''_o = -1.2 - 0.6 = -1.8$ *mv.*
E''_1 [Wilson at 10,000 ohms] $= -1.2 - 0.623 = -1.823$ *mv.*
E''_1 [Wilson at 5,000 ohms] $= -1.2 - 0.644 = -1.844$ *mv.*
E''_1 [Goldberger] $= -1.2 - 0.75 = -1.95$ *mv.*

The voltage error introduced in the aV_R lead by the Wilson and Goldberger methods is:

Wilson method with 10,000 ohm resistors = 1.28 per cent error
Wilson method with 5,000 ohm resistors = 2.44 per cent error
Goldberger method = 8.35 per cent error.

TECHNIQUE

In the registering of unipolar extremity leads with the Wilson central terminal, the exploring wire is commonly attached to the limb electrode which is part of the central terminal circuit. That is, if Lead V_L is desired, the exploring wire is connected to Electrode B of Fig. 5. *This procedure is incorrect and may introduce very serious error in the electrocardiogram.* The correct way to connect the patient is shown in Fig. 5. Instead of connecting the exploring wire

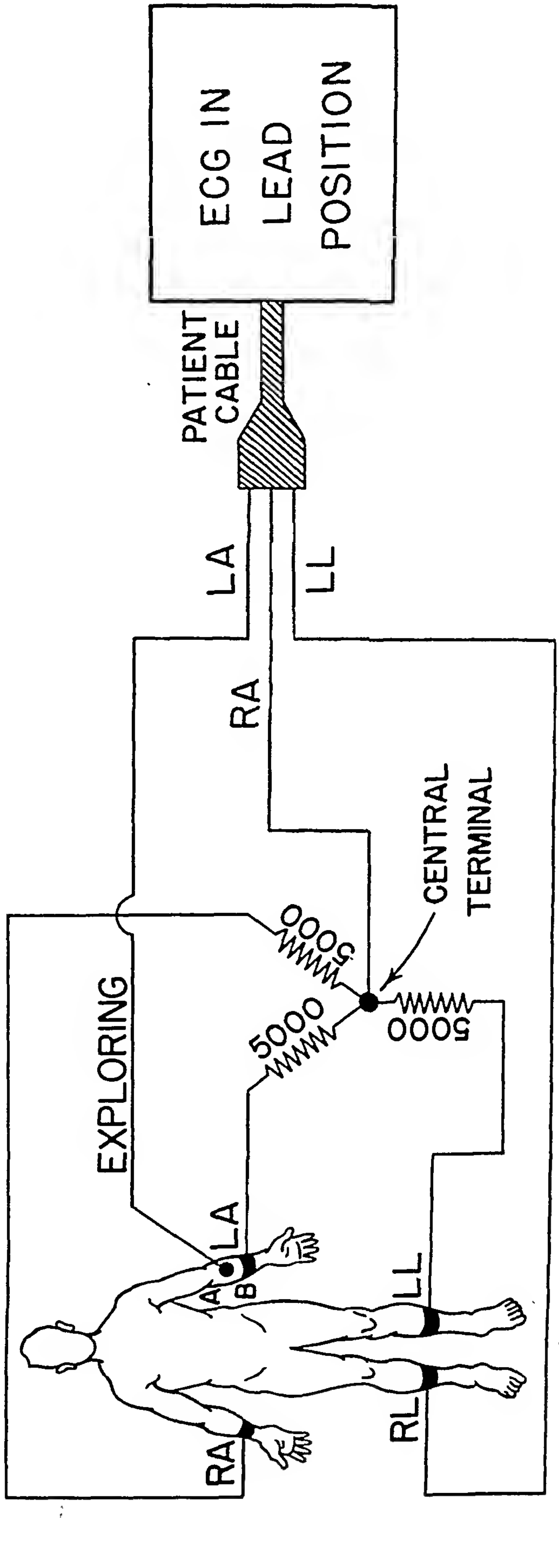

Fig. 5.—Connections for unipolar extremity leads by the Wilson technique.

to Electrode B when registering Lead V_L, another electrode A must be used and the exploring wire attached to it. The spacing between Electrodes A and B is unimportant, but electrode jelly must not be allowed to communicate between the two electrodes. The connection to the right leg is useful for eliminating alternating current interference because several makes of electrocardiographs require that the patient be grounded to the apparatus. In these electrocardiographs the unused limb, such as the left leg in Lead I, the left arm in Lead II, and the right arm in Lead III, is grounded to the apparatus via the lead selector switch. When the Wilson central terminal circuit is employed, the right arm, left arm, and left leg are not available for grounding. The right leg is, therefore, the most convenient portion of the patient to ground.

The magnitude of error that is introduced in the unipolar extremity lead electrocardiograms if the exploring electrode is connected to Electrode B of Fig. 5 may be calculated. Fig. 6 is a circuit which is equivalent to the one shown in Fig. 5 but takes into consideration the skin resistance under all electrodes. As before, let

R_{RA} = resistance of skin under right arm electrode = 1,000 ohms
R_{LA} = resistance of skin under left arm electrode = 2,000 ohms
R_{LL} = resistance of skin under left leg electrode = 3,000 ohms
R_E = skin resistance under Electrode A.

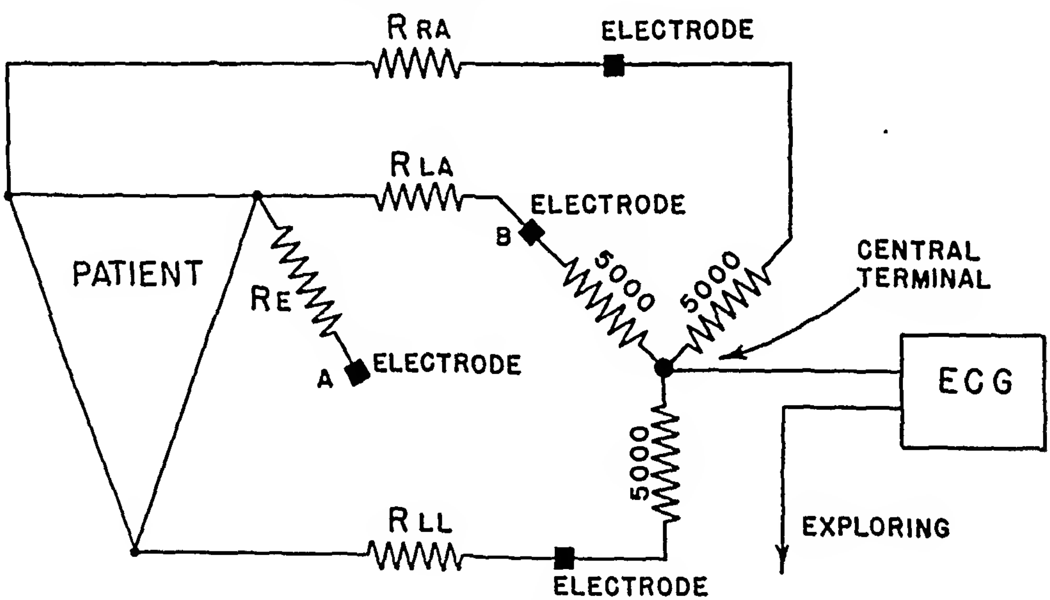

Fig. 6.—Equivalent electrical circuit of Fig. 5 in which the skin resistance under the right arm, left arm, and left leg electrodes are taken into consideration.

If Lead V_L is taken by the method shown in Fig. 5, the action potentials registered by the electrocardiograph of Fig. 6 are formed between the central terminal and Electrode A. This is the actual V_L lead because the effects of R_E are negligible when an electronic electrocardiograph is used,[19] and in a string electrocardiograph the string sensitivity is adjusted to compensate for the effects of resistance in series with it. However, if the exploring wire is placed on

Electrode B of Fig. 5, then Lead V_L is registered between the central terminal of Fig. 6 and Electrode B. If R_{LA} is 2,000 ohms, then Lead V_L is registered with an amplitude equal to five-sevenths the actual value because of the division of the action potential between R_{LA} and the 5,000 ohm resistor. Obviously, the higher the skin resistance under the electrode, the greater is the magnitude of error.

If the Goldberger central terminal were used with the incorrect technique, zero action potential or an isoelectric line would be registered by the electrocardiograph. The correct connections with the Goldberger central terminal are as with the Wilson central terminal.

A natural question which should be considered at this time is the relative accuracies of the Einthoven string galvanometer electrocardiograph and the electronic electrocardiograph when used in conjunction with the Wilson and Goldberger central terminals. When Wilson first described the central terminal, he suggested that a stage of electronic coupling be interposed between the central terminal-patient circuit and the string.

As previously mentioned, any resistance which is placed in series with a string requires a slackening of the string tension. *In a string galvanometer, the galvanometric speed is proportional to the square root of the tension and the tension is proportional to the reciprocal of the sum of the string resistance and any resistance in series with it.* For example, the usual resistance of a string is approximately 2,000 ohms and a well-scrubbed normal patient may attain a resistance of approximately 2,000 ohms which totals 4,000 ohms. Let us assume that the minimum galvanometer speed of the string electrocardiograph under such operating conditions is 0.01 second. Should the patient resistance increase to, say, 6,000 ohms, then the total resistance of the circuit becomes 8,000 ohms. In turn, the string must be slackened so that the new galvanometric speed is reduced to 0.014 second. Lewis and Gilder[18] have shown that galvanometric speeds slower than 0.02 second will produce sluggish and inaccurate electrocardiograms in human beings.

Fig. 7 is the basic circuit of the Wilson central terminal connected to a string galvanometer and patient. As before, the maximum allowable resistance in the circuit so that the galvanometric speed will not be slower than 0.02 second is

$$\frac{0.01}{\sqrt{4000}} = \frac{0.02}{\sqrt{R}}$$

or $\quad R = 16{,}000 \text{ ohms}$

If we subtract the 2,000 ohm string resistance, then 14,000 ohms is allowable for the rest of the circuit resistance. Let us assume that

$$R_E = R_{RA} = R_{LA} = R_{LL}$$

This may be done because the internal resistance of a patient is small compared with the contact resistance. Then

$$\frac{R_E + 5000}{3} + R_E = 14{,}000$$

or $\quad R_E = 9{,}250 \text{ ohms}$

This means that if the contact resistances at the right arm, left arm, and left leg and exploring electrodes do not exceed approximately 9,000 ohms, the galvanometric speed will not be slower than 0.02 second. In practice, such values of resistance are rarely exceeded; therefore, the string electrocardiograph should record clinically accurate unipolar electrocardiograms on human beings from a galvanometric speed standpoint.

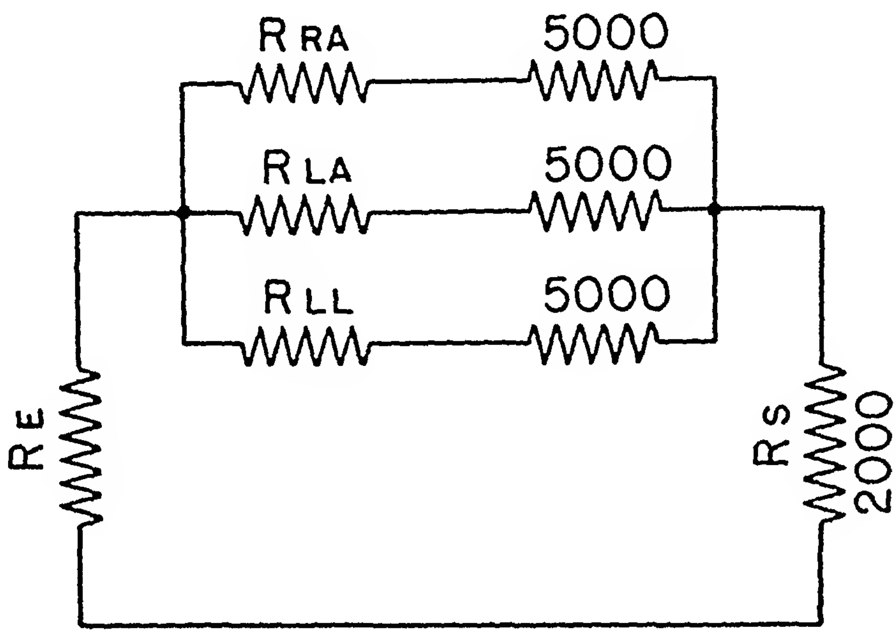

Fig. 7.—Basic circuit of the Wilson central terminal connected to a string galvanometer and patient in which:

R_{RA} = skin resistance under right arm electrode
R_{LA} = skin resistance under left arm electrode
R_{LL} = skin resistance under left leg electrode
R_S = string resistance = 2,000 ohms
R_E = skin resistance under exploring electrode plus internal resistance of patient

Galvanometric speed versus patient resistance is of no consequence in electronic electrocardiographs or when a stage of electronic coupling is used with the Einthoven string galvanometer.[1,2,17]

DISCUSSION

Wolferth and Livezey[5] have differed with Wilson and associates[12] as to the accuracy of the central terminal method for registering unipolar electrocardiograms. They are agreed, however, that an accurate method for registering unipolar electrocardiographic leads would be a most important electrocardiographic method. Wolferth and Livezey state: "It is of vital importance to electrocardiography that if error in matters of this nature exist, such error be recognized. If, on the other hand, there is no important source of error in Wilson's 'unipolar' leads, they should be used for practically all electrocardiographic work."

When Wilson and associates devised the central terminal, they suggested that its accuracy is dependent upon the validity of the equilateral triangle theory and Kirchhoff's laws of electric networks. They claimed that the potential which exists at the central terminal must be equal at every instant to the mean of the potentials at the electrodes on the right arm, left arm, and left leg. Also, if the equilateral triangle theory is 100 per cent valid, the sum of the potentials at the three limbs must total zero and thus the central terminal potential must be equal to zero. Our mathematical analysis shows, however, that the potential at the central terminal may be modified by dissimilar patient resistance in each of the three limbs. Differences in resistance at the three limbs is caused by unlike electrical conductivity of the skin under each of the three extremity electrodes.

Almost everyone is agreed that the equilateral triangle theory of Einthoven, Fahr, and De Waart is not 100 per cent correct. The controversial point is as to the amount of error that may be present. Wilson and his associates state: "In our opinion, there is no reason to suppose either that Einthoven and his associates had any false notions as to the general character of the heart's electrical field or that they considered their method of determining the position of the electrical axis of the heart entirely free of error. In 1921, a paper by Lewis, Drury, and Iliescu[18] on the electrical axis of the auricle in clinical cases of auricular flutter raised a question as to the conditions under which the principles of Einthoven's triangle are applicable. A letter to Einthoven concerning the matter was answered by him on November 21, 1921 as follows:

" 'In regard to the equilateral triangle I fully agree with you. I assumed in my original paper "Ueber die Richtung and die Manifeste Grösse der Potential—schwankungen etc.," in the center of the triangle a "bipole," that is to say, two points lying very close together and showing a potential difference. The triangle was supposed to be a homogenous sheet of conducting material and in regard to the distance between the two points of the bipole, of a large, let us say infinite extent.

" 'The applicability of this scheme to the ordinary leads of the human body depends indeed on the fact that the electrodes are at a relatively great distance from the heart. If they are placed near the heart the errors are greater and the more so the closer they get to the heart. Even in the case of the ordinary leads from the limbs the results cannot be absolutely exact.' "

Several independent investigators[7,8,9,10] who have performed experiments on the cadaver to determine the validity of the equilateral triangle are agreed that the direction and relative magnitude of deflections in the limb leads are within close limits of the relationships expressed in the equilateral triangle theory. Others[11,12,13] have compared the central terminal of the Einthoven, Fahr, and De Waart triangle with other central terminals, each connected to a set of three electrodes located equidistant from the heart and lying at the apices of a triangle enclosing it. All but Wilson and his associates observed that the potential differences between the various central terminals were very close to zero. Wilson and co-workers found that the differences in potential did not exceed 0.15 millivolt. The immersion experiments[12,15,16] showed a greater degree of discrepancy. The

experiments of Wolferth and Livezey, in which they paired an exploring electrode with one placed over the spine of the right scapula and compared it to the Wilson central terminal method, show considerable discrepancy.

Nowhere in the literature which pertains to the validity of the equilateral triangle theory has anyone shown that serious error may have been present in the experiments performed by Fahr and Weber, by Wagner, and by Johnston, Kossmann, and Wilson on cadavers and those of Wilson and Herrmann on the living dog. Until concrete proof is produced that the cardiac action potentials at the limbs deviate a considerable amount from the relationships expressed in the equilateral triangle theory, it is our contention that we are not too far wrong in assuming that a reasonably good similarity exists. That is, experimental data indicate that the deviations of the action potentials at the limbs from values indicated in the equilateral triangle theory are small enough to warrant clinical application of the theory.

By mathematical procedure it can be proved that the principles fundamental to the central terminal circuit are correct for unipolar electrocardiographic applications. This holds true only when the patient resistances in the three limbs are identical. Any dissimilarity of resistance at the three extremities modifies the central terminal potential and, in turn, the unipolar electrocardiogram.

TABLE I. EFFECTS OF DISSIMILAR LIMB RESISTANCE ON V_R LEAD IN A HYPOTHETICAL CASE

METHOD	RA PATIENT RESISTANCE (OHMS)	LA PATIENT RESISTANCE (OHMS)	LL PATIENT RESISTANCE (OHMS)	C. T. POTENTIAL (MILLIVOLTS)	ERROR IN V_R LEAD (PER CENT)
Theoretical	1,000	2,000	3,000	0	0
10,000 ohm Wilson	1,000	2,000	3,000	−0.043	3.59
5,000 ohm Wilson	1,000	2,000	3,000	−0.077	6.42
Goldberger	1,000	2,000	3,000	−0.355	29.5

In Table I are shown the results of our calculations on a hypothetical case when the patient resistance in the right arm due to skin resistance is 1,000 ohms, in the left arm, 2,000 ohms, and in the left leg, 3,000 ohms. In clinical electrocardiography, it is not unusual to obtain even larger resistance differentials at the limbs.[21] Note how the central terminal potential deviates from the theoretically correct value by the use of the Wilson and Goldberger techniques. Obviously, *the higher the value of the three fixed resistors, the less is the deviation of the central terminal voltage from zero.* Because the central terminal voltage deviates from zero, the error present in the Wilson circuit with 10,000 ohm resistors is 3.59 per cent, and when 5,000 ohm resistors are employed the error is increased to 6.42 per cent; but when the Goldberger technique is employed, the error jumps to 29.5 per cent. In clinical electrocardiography an error of 6.42 per cent may not be too serious, but 29.5 per cent is enormous. *Similarly, the magnitude of*

error in unipolar chest leads due to the deviation of the central terminal voltage would be of the same order of magnitude.

Dissimilar patient resistance in the limbs does not produce as much error in the augmented unipolar extremity leads as occurs in the unipolar extremity leads and in the unipolar chest leads. In Table II are shown our calculated errors in the aV_R lead by the Wilson and Goldberger techniques. It so happens that the left arm patient resistance in this case was 2,000 ohms and the left leg was 3,000 ohms. However, more error would be present if the left arm resistance were 1,000 ohms and the left leg resistance unchanged. Such a resistance combination occurs in the aV_L lead on this hypothetical patient. For comparison purposes we merely interchange the limb resistances and calculate the new value of aV_R error which is given in Table III. Under the more severe condition of limb resistance represented in Table III, the error in the Goldberger method is 8.38 per cent, as compared to 2.44 per cent when the Wilson method with 5,000 ohm fixed resistors is used and 1.28 per cent with 10,000 ohm fixed resistors.

TABLE II. EFFECTS OF DISSIMILAR LIMB RESISTANCE ON aV_R LEAD IN A HYPOTHETICAL CASE

METHOD	LA PATIENT RESISTANCE (OHMS)	LL PATIENT RESISTANCE (OHMS)	ERROR IN aV_R LEAD (PER CENT)
Theoretical	2,000	3,000	0
10,000 ohm Wilson	2,000	3,000	0.67
5,000 ohm Wilson	2,000	3,000	1.1
Goldberger	2,000	3,000	3.3

TABLE III. EFFECTS OF DISSIMILAR LIMB RESISTANCE ON aV_R LEAD IN A HYPOTHETICAL CASE

METHOD	LA PATIENT RESISTANCE (OHMS)	LL PATIENT RESISTANCE (OHMS)	ERROR IN aV_R LEAD (PER CENT)
Theoretical	1,000	3,000	0
10,000 ohm Wilson	1,000	3,000	1.28
5,000 ohm Wilson	1.000	3,000	2.44
Goldberger	1,000	3,000	8.35

By similar mathematical procedure, the magnitude of error present in augmented extremity leads and unipolar chest and limb leads for various combinations of skin resistance in the three limbs may be calculated. This would be a rather lengthy procedure and is beyond the scope of this paper.

By mathematical approach we have shown that the higher the resistances in the central terminal circuit, the less is the error that may be introduced by

dissimilar contact resistance at the limbs. Wilson appreciated this fact when he first used 25,000 ohms but discarded this value in favor of 5,000 ohms because of alternating current interference. By more modern electrical techniques, central terminal resistances of 200,000 ohms may be used with a negligible increase of interference pick-up. This is especially important when registering simultaneous unipolar leads or unipolar leads in conjunction with bipolar leads. The simultaneous registration of unipolar leads has been neglected and is much needed for a better understanding of the mechanism of production of these leads.

CONCLUSIONS

1. The experiments of Fahr and Weber, of Wagner, and of Johnston, Kossmann, and Wilson on cadavers and those of Wilson and Herrmann on the living dog show that the cardiac action potentials at the right arm, left arm, and left leg are a very close approximation of the values expressed in the equilateral triangle theory of Einthoven, Fahr, and De Waart. To our knowledge, nowhere in the literature has anyone shown that serious error may have been present in these experiments. It is our contention, therefore, that we cannot be too far wrong in assuming that the deviation of the action potentials at the limbs from the values indicated in the equilateral triangle theory are small enough to warrant clinical application.

2. When Wilson, Macleod, and Barker suggested the central terminal method for registering unipolar electrocardiograms, they stated that the accuracy of the method is dependent upon the validity of the equilateral triangle theory and Kirchhoff's laws of electric networks. We have found that dissimilarity of skin resistance under the extremity electrodes which comprise the central terminal are an important additional factor.

3. It may be shown by mathematical approach that the potential at the Wilson or Goldberger central terminal is zero *only* under the following conditions:

A. If the equilateral triangle theory is 100 per cent correct.

B. If the skin resistances under the extremity electrodes which comprise the central terminal circuit are identical in value.

4. If the voltages at the limbs deviate a slight amount from the values expressed in the equilateral triangle theory, the central terminal potential is slightly removed from zero and the unipolar electrocardiogram is modified slightly.

5. Dissimilarity of skin resistance under the three extremity electrodes is unavoidable in clinical electrocardiography. The use of fixed resistors as suggested by Wilson, Macleod, and Barker minimizes the degree of error. The Goldberger central terminal does not employ the three fixed resistors but depends upon the skin resistance only. Therefore, additional error may be introduced when the Goldberger technique is used for registering unipolar electrocardiograms.

6. The Wilson central terminal may be used for registering augmented unipolar extremity leads. The basic principle is exactly the same as that suggested by Goldberger.

7. Dissimilar skin resistance under the extremity electrodes which comprise the augmented central terminal does not introduce as much error in the augmented unipolar extremity leads as occurs in unipolar extremity leads and unipolar chest leads.

8. Error in the augmented unipolar extremity leads due to dissimilar skin resistance under the extremity electrodes is less with the Wilson central terminal than with the Goldberger technique.

9. If the Wilson central terminal is used for registering unipolar extremity leads, the exploring wire must be applied to an electrode other than the one which forms the central terminal. The separation between the two electrodes is unimportant. Electrode paste must not communicate between the electrodes. If the Goldberger central terminal is used, the procedure is the same. Application of the exploring wire to the electrode which forms the Goldberger central terminal will register an isoelectric line, whereas the Wilson central terminal will register an augmented unipolar extremity lead which is reduced in magnitude.

10. If precaution is used in the scrubbing of the patient, the Wilson 5,000 ohm central terminal, operating in conjunction with an Einthoven string electrocardiograph, will register reasonably accurate unipolar leads.

11. Error may be introduced in unipolar electrocardiographic leads if the Goldberger central terminal is used. As far as we can see, there are no obvious advantages in eliminating the fixed resistors which make up the central terminal. The technique for registering augmented unipolar extremity leads suggested by Goldberger has definite merit, but better results are obtained theoretically if Goldberger's technique is used with the Wilson central terminal.

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TRANSIENT VENTRICULAR FIBRILLATION

II. The Effects of Gradually Induced Oxygen Deficiency on Patients With Transient Ventricular Fibrillation and on Patients With Periodic Standstill of the Ventricle

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THE purpose of this study was to determine the effects of gradually induced oxygen deficiency on patients subject to transient seizures of ventricular fibrillation. The alterations in the rhythm of the heart following anoxemia in such patients were compared with the changes in the cardiac mechanism of patients with auriculoventricular dissociation subject to recurrent attacks of standstill of the ventricles. Since the immediate factors that initiate transient seizures of ventricular fibrillation are still unknown, it was hoped that these experiments would yield some data on the coefficients responsible for this unusual mechanism in man.

REVIEW OF LITERATURE

Experimental Observations.—It is well established from experimental observations that in the resting animal the earliest effects of anoxia on the heart result in an acceleration of the sinus rate.[1,2] Wiggers[3] has recently pointed out that a progressive decrease in the respired oxygen volumes to about 12 per cent (which period he calls *hypoxia* and which corresponds to arterial blood oxygen saturation of about 75 per cent) always increases the flow of blood by redistribution of blood flow and by cardiac acceleration. He attributes the increased cardiac rate to a decreased vagal tone, and perhaps to some direct effect on the sinoauricular node. When the oxygen in the inspired air falls below 12 per cent (which he calls the "true period of anoxia"), a greater stroke volume occurs, there is a further increase in the velocity of ejection, and the economy of effort is enhanced. When the oxygen declines to 7 or 6 per cent, which corresponds to an oxygen saturation of the arterial blood between 50 and 35 per cent, a coronary crisis occurs. The arterial pressure declines abruptly, the pulse pressure is reduced, the systolic pressure decreases, the venous pressure rises greatly, and various types of *conduction and rhythm* disturbances may occur.

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The delayed conduction of the normal cardiac impulse with progressively developing A-V dissociation has been attributed to the direct effect of the asphyxial state upon the A-V mechanism of the heart.[4,5] It was found to be independent of the action of the vagus nerves, for it occurred in the atropinized animal as well as after section of the vagi.[6,7] In this state of anoxemia, the sinoauricular node of the mammalian heart was found to be as sensitive as the bundle of His.

Resnik[3] also observed a predisposition of the auricles to fibrillate when these chambers of the heart were stimulated by a direct current in the presence of anoxia. He pointed out that a damaged heart, when subjected to anoxemia, may exhibit early a functional disturbance which will appear only in the presence of a more profound anoxemia in the normal heart. Both Resnik[8] and Criep[9] noted a definite tendency of the *ventricles to fibrillate* after the establishment of the various grades of block that appeared in the advanced stages of oxygen want. In Criep's studies, ectopic ventricular beats preceded ventricular fibrillation in the presence of both auricular and ventricular standstill, while auricular fibrillation appeared as an early manifestation. These profound alterations in the rhythm of the heart were found not only after the animal was deprived of an adequate amount of oxygen, but also in the course of anaphylactic reactions that ended in death.

Clinical Observations.—There are ample correlated observations on the effects of gradually induced oxygen want on the RS-T segments and the T waves of the electrocardiograms of individuals with normal hearts as well as on patients with angina pectoris, coronary insufficiency, and myocardial disease.[10,11] In the majority of effective responses to this form of anoxia, the electrocardiograms reveal a lowering of the RS-T segment below the isoelectric line and eventually a final negativity of T waves. However, there is only a single study in the literature in which abnormal rhythms of the heart were emphasized as a finding during "extreme" oxygen want.

In studying the response of the circulation in men to gradually reduced oxygen tension, Greene and Gilbert[15] observed an acceleration of the sinus rate during the earliest phases of oxygen reduction. This was usually followed by a marked sinus arrhythmia with a decrease in the amplitude of the main ventricular deflections and the size of the T waves. A slowing of the sinus rate followed this acceleration, in which the rate was lowered from an average of 110 beats per minute to 80 beats before there appeared the various grades of A-V conduction disturbances leading to partial and complete heart block. Occasionally there was standstill of the auricles. A drop in blood pressure observed at this stage of anoxemia was found to be independent of the changes in the rate and rhythm of the heart. Note should be made here that in four normal individuals the appearance of these far-advanced abnormal rhythms coincided with loss of mental attention, appearance of cyanosis, changes in respiration, loss of voluntary control, and, finally, loss of consciousness. All of these signs were transitory and disappeared immediately when the mask was removed.

METHOD OF STUDY

Two patients who were experiencing transient seizures of ventricular fibrillation and two patients with periodic standstill of the ventricles form the subjects of this study. In one patient recurring attacks of transient ventricular fibrillation appeared after the development of transient periods of A-V dissociation in the course of a normal sinus mechanism. The other three patients had established A-V dissociation.

These experiments were carried out at a time when it was certain that the patients had not had any changes in their cardiac mechanism for at least forty-eight hours. It was definitely determined from both a study of the heart and pulse rates, while the patients were connected to the electrocardiographic circuit, that the basic ventricular rate was fairly constant prior to the onset of the experiments, that is, that it did not vary more than five beats per minute. Two patients were in bed constantly and two were ambulatory. No drugs were administered for at least one week prior to these studies. All four patients had mild signs of congestive heart failure with shortness of breath and three had cyanosis of the lips and nail beds.

One method of rebreathing was identical to that used by others in similar experiments.[15] The subject was placed in a reclining position and connected to a basal metabolism machine filled with room air and the carbon dioxide was removed by soda lime. Another method consisted of having the subject rebreathe in a small canvas bag filled with room air without the removal of the carbon dioxide. Continuous electrocardiograms were recorded prior to, during, and subsequent to the rebreathing periods.

The experiments were terminated when such signs were observed as loss of mental attention and sustained voluntary control, intense cyanosis, or abnormal changes in the type of breathing.

RESULTS

The Effects of Anoxemia on Patients With Transient Ventricular Fibrillation.—One woman showed a sinus rhythm and developed transient seizures of ventricular fibrillation after the onset of A-V dissociation. Rebreathing for only four minutes and thirty-seven seconds changed her sinus mechanism to one of heart block with the auricles beating 78 per minute and the ventricles 32. This type of A-V dissociation persisted after the termination of the experiment for several days before there was a return to the sinus mechanism. It is of interest to note that the heart block could also be readily induced in this patient by the intramuscular injection of epinephrine hydrochloride[16] as well as by the intravenous injection of digitalis bodies.[17]

In this woman and in another patient the effects of rebreathing were variable when the A-V dissociation had already been established. In the first case, rebreathing either in the basal metabolism machine or in the bag yielded no change in the cardiac rhythm except a slight acceleration of the auricles at the end of seventeen minutes when the experiment had to be discontinued because of discomfort. The ventricular rate remained unchanged.

In the other patient rebreathing was followed in the first four minutes by an acceleration of the basic auricular rate from 88.3 beats per minute to 100 beats. The ventricular rate in the meantime increased to 32.6 beats from a previous average of 30.7 beats (Fig. 1,*A* and *B*). At seven and nine minutes, respectively,

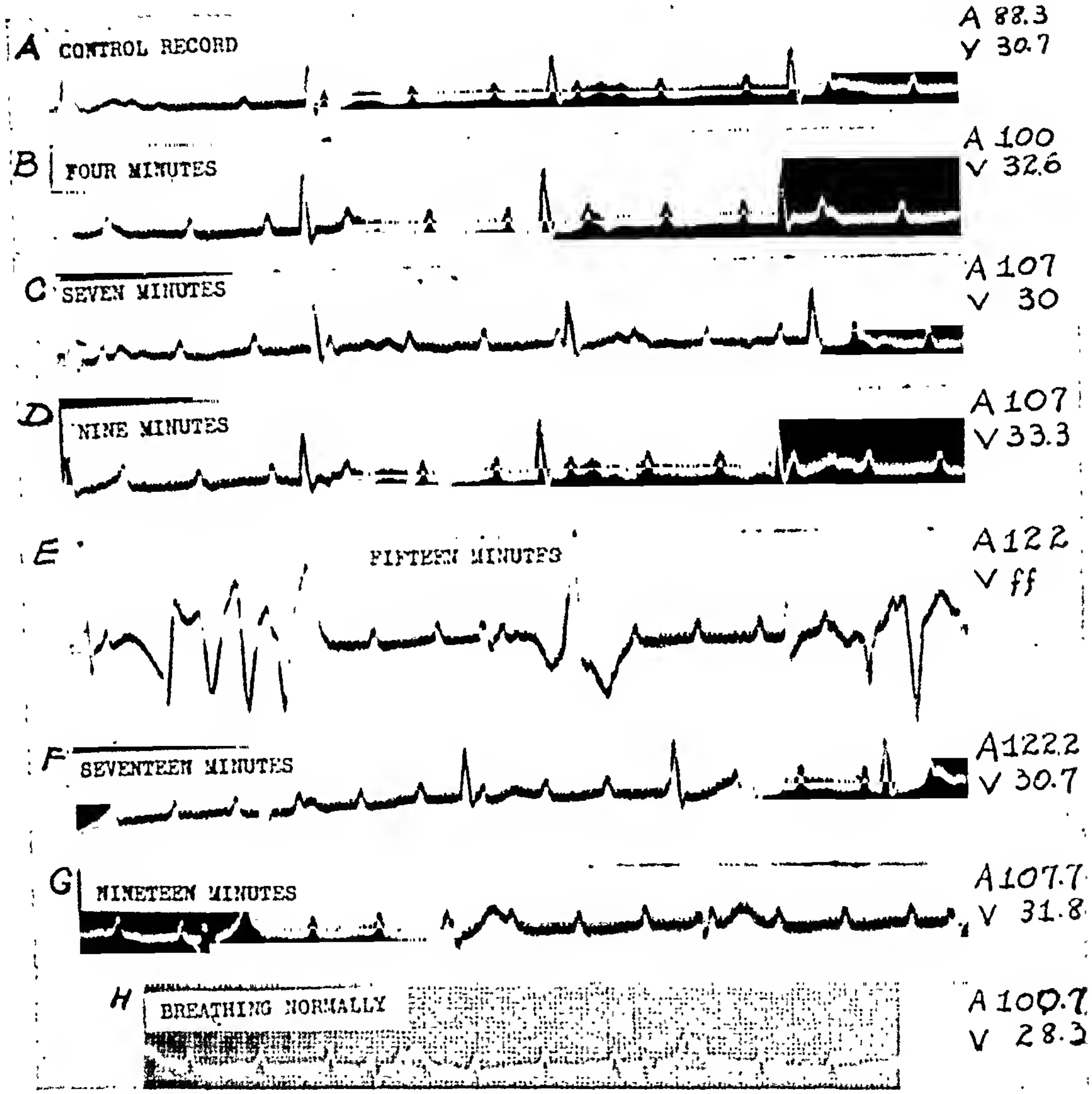

Fig. 1.—The successive alterations in the cardiac mechanism following rebreathing in a patient with A-V dissociation subject to *transient seizures of ventricular fibrillation*. Note the progressive increase in the auricular rate and the development of a short run of ventricular fibrillation, fifteen minutes after rebreathing (*E*).

after rebreathing, the auricles beat at the rate of 107 per minute and the ventricles increased to 30 beats (Fig. 1,*C* and *D*). Fifteen minutes after rebreathing, the auricular rate suddenly increased to 122.2 beats per minute and the basic ventricular rate was interrupted at first by single and then by alternate premature beats of the ventricles and finally by large aberrant ventricular oscillations that

resembled in every respect the prefibrillatory period observed in this patient prior to the onset of syncopal attacks due to transient ventricular fibrillation.[18] The basic ventricular complexes were also aberrant, as compared with the deflections present before the onset of the experiment. Two minutes after the removal of the mask, the auricular rate was still 122.2 beats per minute, but the ventricular rate now averaged 30.7 beats and the rhythm was perfectly regular (Fig. 1,*F*). The ventricular complexes now resumed their original size and form. However, within two minutes, that is, nineteen minutes after the onset of the experiment, they changed shape again and became aberrant, even though the patient was breathing room air. The auricles then slowed to 100.7 beats and remained at this rate with a regular rhythm although the ventricles were now beating at only 28.3 beats (Fig. 1,*H*). This type of cardiac mechanism persisted for several hours when finally there was a return to the same rate and rhythm that was present at the beginning of the experiment.

Throughout the entire period of observation this patient did not lose consciousness and his only complaint was a slight precordial pain that set in with the appearance of the ventricular irregularities. The pain disappeared when the mask was removed.

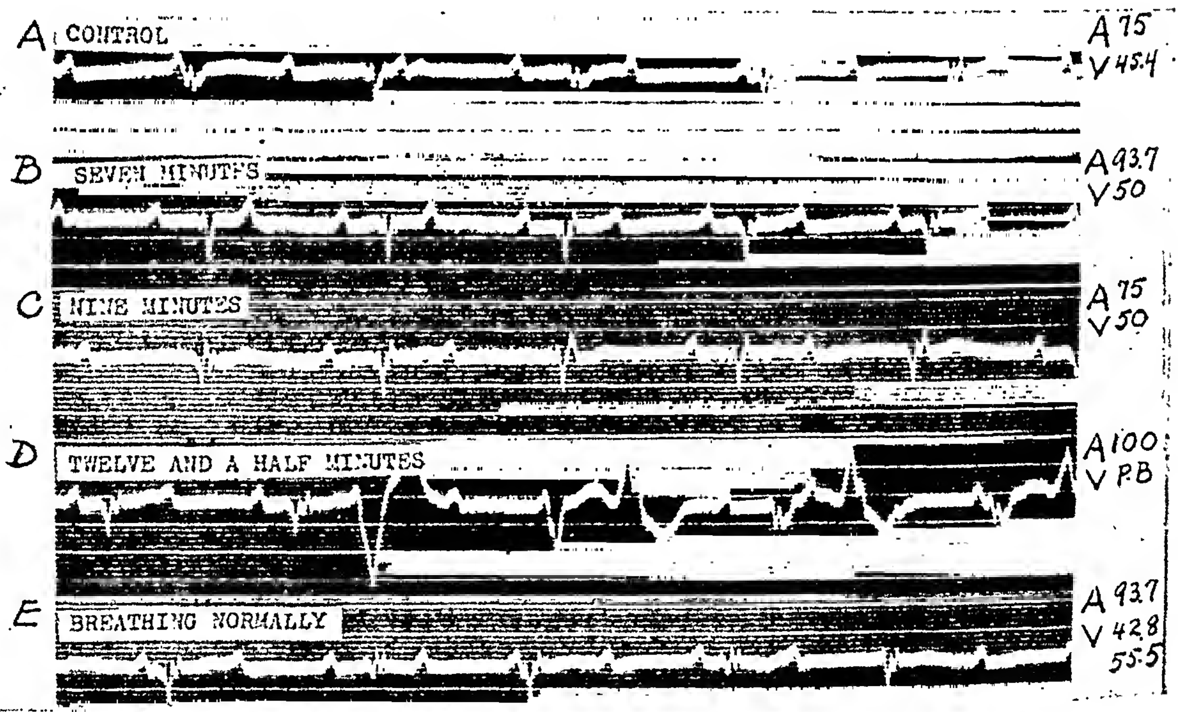

Fig. 2.—The successive alterations in the cardiac mechanism following rebreathing in a patient with A-V dissociation subject to periodic standstill of the ventricles. Note the increase in the auricular and ventricular rates and the development of premature beats of the ventricles (*D*).

The Effects of Anoxia on Patients With Periodic Standstill of the Ventricles.—In an ambulatory patient with periodic standstill of the ventricles in the course of established A-V dissociation, rebreathing for seven minutes in the basal metabolism machine increased the basic auricular rate from 75 beats per minute to 93.7 (Fig. 2,*A* and *B*). The basic ventricular rate was accelerated from 45 to

50 beats per minute. There was no essential change in the shape, size, or form of the basic ventricular deflections, which were of two distinct types, in the intervals when the patient was free from periodic standstill of the ventricles.

After nine minutes of rebreathing, the auricular rate slowed to 75 beats per minute (Fig. 2,*C*) and increased again within three and one-half minutes to 100.7 beats. Now the basic ventricular rhythm was interrupted by alternate premature beats of the ventricles and there was an increase in the width of the basic ventricular complexes which became markedly aberrant, as compared with previous deflections of the ventricles (Fig. 2,*D*). At this time the patient complained of pains in his chest, but he was not conscious of any change in his heart rhythm. His breathing was accelerated; there was a general increase in his cyanosis; and he asked to have his mask removed.

Immediately the premature beats of the ventricles and the aberrant ventricular complexes disappeared abruptly. However, for the next few minutes there set in a peculiar irregularity of the ventricles in the presence of a regular auricular rhythm with the auricles beating at 93.7 beats per minute. The ventricular rate varied from 42.8 to 55 beats per minute. A coupled rhythm was present in which the alternate sphygmic intervals between the basic ventricular complexes were equal to each other (Fig. 2,*E*). The ventricular deflections were variable in shape and size from beat to beat. This type of abnormal irregularity persisted for seventeen minutes before there was a return to the basic rate and rhythm which was present before the beginning of the experiment.

In another patient with periodic standstill of the ventricles, rebreathing room air in a bag for sixteen minutes on one occasion and thirteen minutes on another, without the elimination of carbon dioxide by soda lime, resulted in a transient acceleration followed by a temporary slowing of the auricular rate, but there was no change in the rate or rhythm of the ventricles, which did not vary more than three beats per minute throughout the experiment.

DISCUSSION

These observations reveal that patients who are subject to transient seizures of ventricular fibrillation easily develop A-V dissociation when anoxia is induced in them by the rebreathing method in the presence of normal sinus rhythm. After the appearance of either transient or permanent A-V dissociation, progressively increasing oxygen want results in the development of short, recurring, and widely aberrant ventricular oscillations, which in their final analysis are short runs of ventricular fibrillation. In the patients observed in this study, these profound alterations in the rhythm of the heart appeared much earlier in the course of oxygen want than they did in normal individuals.[15] This is likely due to the fact that these patients already had signs of mild congestive heart failure when the experiments were begun. It is known that congestive heart failure is accompanied by a lowered arterial and venous concentration of oxygen.[19,20] Peters and Barr[21] have observed changes in the dissociation curve for carbon dioxide and in hydrogen ion concentration of the blood in advanced heart failure, and Siebeck[22] noted unequal pulmonary expansion in cardiac insufficiency resulting in an imperfect mixture of gases in the lungs.

That progressive oxygen want is directly responsible for these abnormal ventricular irregularities may be gained from the simultaneous effects produced on the rate and rhythm of the auricles. There is at first an acceleration of the auricular rate and then at times there follows a transitory slowing. Occasionally, with increased anoxemia, there is a progressive acceleration of the auricles. This may be present for some time after rebreathing is stopped. The behavior of the auricular rate and rhythm during A-V dissociation is identical with that observed in anoxic experiments on individuals with normal sinus rhythm. It indicates that the changes in ventricular rate and rhythm must be due to the same operating factor, that is, reduced oxygen tension, and not to fortuitous circumstances.

In comparison with these changes, it was noted that in patients in whom standstill of the ventricles was responsible for recurring syncopal attacks, rebreathing initiated only isolated premature beats of the ventricles, at times in the form of a bigeminal rhythm. Occasionally anoxemia influenced the A-V pacemaker so as to accelerate the ventricular rate irregularly.

These arrhythmias of the ventricles following anoxemia suggest the possibility of using the rebreathing method for making a differential diagnosis of the underlying cardiac mechanism responsible for syncopal attacks in patients with A-V dissociation. In patients in whom standstill of the ventricles is the cause of syncopal attacks, rebreathing should result in the appearance of only isolated premature beats of the ventricles. In patients in whom transient ventricular fibrillation is the underlying cardiac rhythm, rebreathing should result in the appearance of short runs of ventricular fibrillation.

Unfortunately, these experiments reveal a marked inconstancy in the response of the diseased human heart to progressively increasing oxygen want. In the same patient on some occasions rebreathing for only a very short period (four minutes) yielded profound disturbances in rhythm, whereas at other times longer periods of rebreathing (nineteen minutes) resulted in no changes at all. Furthermore, the presence of anginal pains following these tests and the general discomfort that rebreathing entails in an already breathless patient, makes this method an impractical test for this type of differential diagnosis.

It is of some interest to speculate on the reasons why only those patients who are subject to transient seizures of ventricular fibrillation should respond to anoxemia with the appearance of a prefibrillatory period and ventricular fibrillation. It certainly cannot be due to the pathologic conditions present in the hearts of these patients, for they all show some form of arteriosclerosis of the coronary arteries. It is established that the ischemia resulting from such coronary insufficiency enhances the tendency to develop ectopic foci.[23,24] Anoxemia, as these observations prove, likewise facilitates the appearance of ectopic foci in the ventricles during all forms of A-V dissociation. It is possible that in patients subject to transient seizures of ventricular fibrillation, anoxemia may enhance myocardial irritability sufficiently so that these ectopic foci become effective when they fall during the "vulnerable phase" of an ectopic beat and thus initiate fibrillation.[25] In this respect anoxemia may be said to be one of the coefficients responsible for the development of ventricular fibrillation in man.

SUMMARY AND CONCLUSIONS

1. Anoxemia was induced by the rebreathing method in two patients who were subject to transient seizures of ventricular fibrillation and in two patients with periodic standstill of the ventricles during auriculoventricular dissociation.

2. In one patient who developed transient ventricular fibrillation during transient A-V dissociation, progressive oxygen want easily converted a normal sinus mechanism to one of A-V dissociation. In two patients, further rebreathing during established A-V dissociation resulted in an acceleration of the auricular rate and the development of short runs of ventricular fibrillation.

3. In two patients who were known to have syncopal attacks due to periodic standstill of the ventricles, rebreathing resulted in an acceleration of the auricles with the appearance of premature beats of the ventricles. Occasionally the A-V rate became more rapid and irregular.

4. The appearance of these arrhythmias following rebreathing was irregular and varied from four to nineteen minutes after the beginning of the experiment.

5. Anoxemia is one of the factors responsible for the development of transient seizures of ventricular fibrillation in patients who are subject to such seizures during A-V dissociation.

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ON T WAVES NORMAL IN SIZE AND DIRECTION BUT ABNORMAL IN CONTOUR

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Many different abnormalities of the QRS complexes have been described, and a large number of these are easily recognized and have been shown to have a more or less precise significance. On the other hand, the different abnormalities of the T complex that have come to be widely recognized as distinctive and as having a definite connotation are few. Abnormalities in the direction of the T wave have received a great deal of attention and several different varieties of inverted T waves are distinguished. Abnormalities of the size of upright T waves have also been described, although these are recognized with greater difficulty than abnormalities in the direction, and their meaning is less clearly understood. Comparatively little has been done toward the analysis of abnormalities of the shape of upright T waves, although it is known, for example, that potassium retention in some cases of uremia may give rise to a tall, pointed T wave of more or less distinctive outline.[1,2]

The purpose of this article is to call attention to certain types of upright T waves which differ in shape from normal T waves and become inverted under a variety of circumstances, alike in certain particulars.

MATERIAL AND METHODS

We have examined 100 normal electrocardiograms collected by Bryant.[3] The ages of the subjects studied by him ranged from 19 years to 32 years. He recorded the standard and unipolar limb leads and precordial Leads V_2 and V_4. We have taken in Lima and in Ann Arbor 100 additional electrocardiograms on normal subjects 20 to 75 years of age. This series includes seven precordial leads (V_1, V_2, V_3, V_4, V_5, V_6, and V_E), as well as the six limb leads. In 80 of these 100 cases the effect of carotid sinus massage was investigated. In forty instances, all of the thirteen leads mentioned were taken before, and at least Leads I, II, V_R, V_F, V_3, V_4, V_5, and V_6 were taken during this procedure. In the remaining forty cases it was studied in a smaller number of leads. The age of the subjects upon which this test was performed ranged from 20 to 75 years, with an average age of 37 years. The effect of carotid sinus massage upon the form of the T wave

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was also studied in a series of 600 patients with various types of heart disease. In this group, tracings were taken only when inspection of movements of the galvanometer string shadow indicated that changes were taking place. Blood pressure readings were taken during the period of carotid sinus stimulation in many instances. When this procedure produced changes in form of the T wave the patient was kept under observation and additional tests were made during a period which varied from a few months to one and one-half years. All electrocardiograms were taken with the patient in the recumbent position. The precordial points from which leads were taken were carefully marked. All records were taken with an electrocardiograph of the string galvanometer type.

OBSERVATIONS

The T Waves of Normal Subjects.—In describing the T waves of the normal records, we may ignore the variations in the polarity and contour of this deflection in Lead III and in Leads V_L and V_1, which are well known. We may also pass over variations of like kind in Leads V_F, V_2, and V_E. The form of the T wave in the remaining leads (I, II, V_R, V_3, V_4, V_5, and V_6) was much more constant.

In all these leads, except V_R, the normal T wave is upright and has a more or less characteristic shape. The slope of its ascending limb is much more gradual than that of its descending limb (Fig. 1,*A* to *E*). The normal T wave of Lead V_R would have the same shape if its direction were reversed (Fig. 1,*F*). The difference between the two limbs of the T wave is well brought out by dropping a perpendicular upon the base line from the apex of this deflection. The angle made with this perpendicular by the tangent of the first limb is much larger than that made by the tangent of the final limb (Fig. 1,*A* to *F*). These angles were measured in approximately forty cases. Their absolute and relative magnitudes vary greatly with the height and the shape of the apex of the T wave. For that reason we shall not present a detailed analysis of these measurements.

In the vast majority of instances both limbs of the T wave were smooth and the changes in their slopes from point to point were gradual. The final slope was often followed by a U wave of small size. In ten normal subjects, 5 per cent, the T waves in one or more leads did not correspond to this description. In some cases the two angles mentioned were approximately equal, the peak of the T wave was unusually sharp or unusually blunt, notching was present, or some other peculiarity in form occurred. Unusual oscillations at the very end of the T wave, possible U waves, sometimes were observed. Because T waves showing these features occurred in only a small percentage of cases, we consider them atypical (Fig. 1,*G* to *X*).

Atypical T Waves in the Electrocardiograms of Patients With Various Diseases.—In the tracings of patients with heart disease, atypical T waves were much more frequent than in the records of normal subjects, and the atypical features were much more pronounced. In many electrocardiograms of such patients the atypical T waves were frequently the only peculiarity suggesting that the heart was abnormal. We have, however, no reliable statistical data upon which an

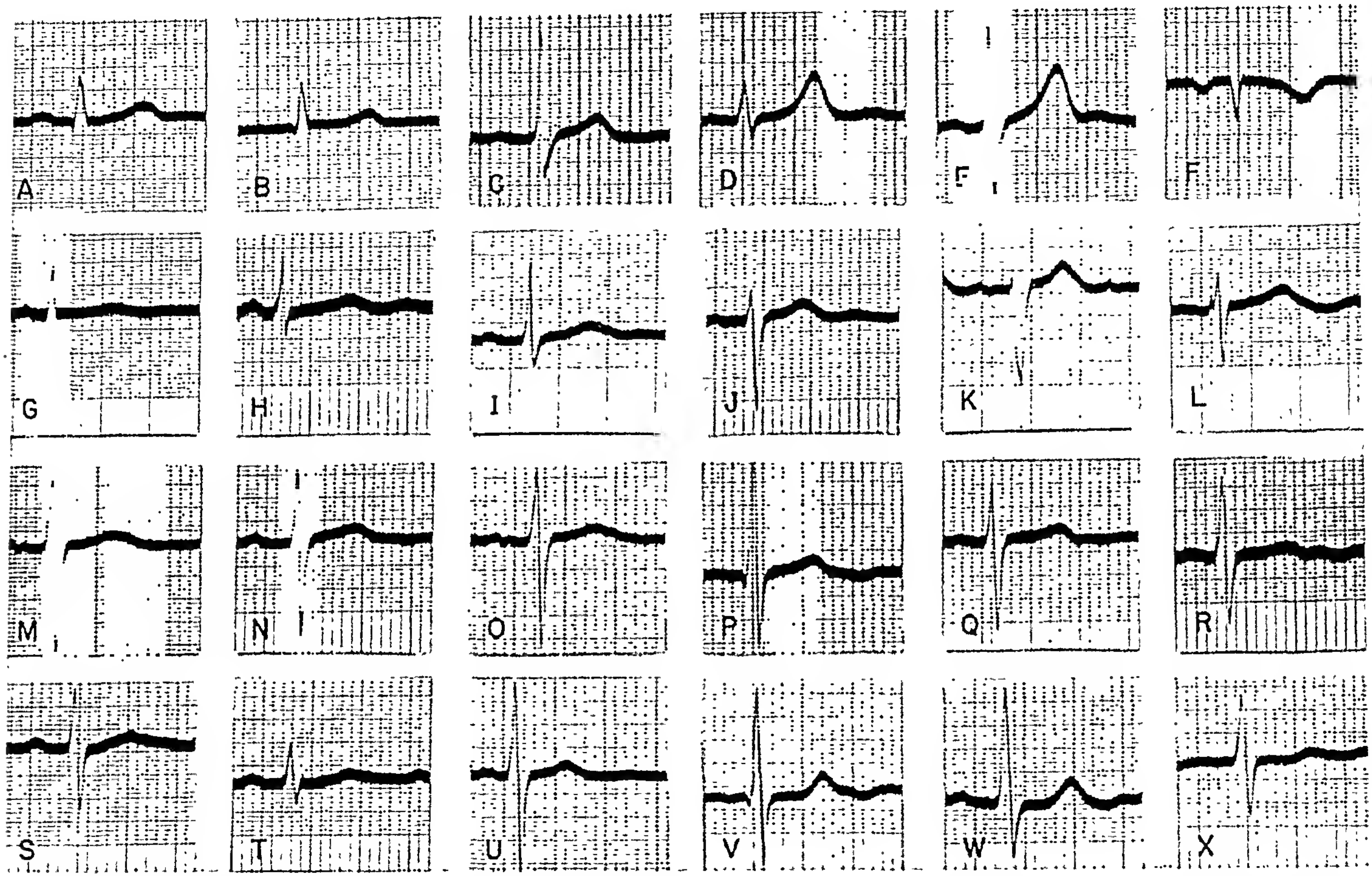

Fig. 1.—The T waves of the complexes shown in Strips *A* to *F*, inclusive, are regarded as normal in shape. The inverted T wave of Strip *F* illustrates the normal appearance of this deflection in Lead V_R. The T waves of the remaining strips, *G* to *X*, inclusive, are regarded as atypical in shape. In some instances the two angles made by the tangents of the ascending and the descending limbs of the T deflection with a perpendicular to the isoelectric level drawn through the summit of this deflection are approximately equal (*G, H, I, J, M, S, T, U, V,* and *W*), or the angle made with this perpendicular by the tangent to the descending limb is larger than that made by the tangent to the ascending limb (*K* and *L*). In other instances the apex of the T wave is usually sharp (*V*) or unusually blunt (*G* and *M*). In still other cases there is an irregularity or notch on the descending limb of the T deflection (*O*). In such cases carotid sinus pressure may cause inversion beginning in the vicinity of the notch or irregularity. Sometimes there are oscillations at the very end of the T wave (*P, Q,* and *R*) which differ in character from the normal U wave. Carotid sinus stimulation often produces inversion beginning near the very end of the T wave under these circumstances.

accurate estimate of the frequency of atypical T waves in tracings of patients with heart disease can be based. They were encountered under a variety of conditions. They occurred in precordial leads taken from points near those which yielded inverted T waves, and were found in tracings taken during attacks of angina pectoris[4] and in tracings taken after exercise tests.[5] Similar deflections were found in the tracings of patients who were convalescing from acute illness or who were suffering from a severe metabolic disorder, frequently when the heart was known to be involved. Atypical T waves often seemed to be associated with a prolongation of the Q-T interval, but in many such instances the end of the T waves could not be determined with sufficient accuracy to make it possible to measure this interval satisfactorily.

Carotid Sinus Stimulation.—In normal subjects carotid sinus stimulation produced slight variations in the amplitudes and contour of the T wave. In no instance did it alter the polarity of this deflection. The maximal change in amplitude was 1.1 mm. and the average change was 0.2 millimeter. In 52 per cent of the cases no modifications of the T wave were observed. Naturally, bradycardia occurred in practically all instances.

In the electrocardiograms of patients with cardiac abnormalities inverted T waves often became more inverted during carotid sinus massage. In only two cases did such T waves become upright. In Lead V_R, in which the T wave is normally inverted, any change which occurred was opposite in character to those which took place in the leads from the left side of the precordium. Atypical upright T waves of the kind described in the preceding paragraph often became inverted during carotid sinus stimulation. Sometimes the inversion was confined to the terminal part of the deflection and was of the V-shaped type. We may leave out of consideration here such changes in the T waves as accompanied the development of an independent ventricular rhythm. This phenomenon seldom occurred.

Carotid sinus massage induced, of course, both bradycardia and a fall in the blood pressure. It is impossible to say whether the T-wave changes observed were due directly to the change in the heart rate, to the change in the blood pressure, or to these combined with other factors.[6,7] In many cases of chronic heart disease in which T-wave changes were observed following carotid sinus stimulation, serial electrocardiograms were taken over a period of several months. In some of the instances in which carotid sinus stimulation produced temporary inversion of previously upright T waves, persistent inversion of these deflections was observed days or weeks later. In other cases, T waves which were persistently inverted when the patient was first seen became upright later, and in many such instances temporary inversion could then be induced by carotid sinus stimulation. We may, therefore, say that carotid sinus stimulation frequently produces temporary changes in the T waves of the kind that will become persistent subsequently, or temporary T-wave changes of a kind that were persistent in the past.[6]

The leads in which the T waves became inverted on carotid sinus stimulation were rather constant for the same individual, but varied from one patient to another. This suggests that the phenomenon under consideration is determined

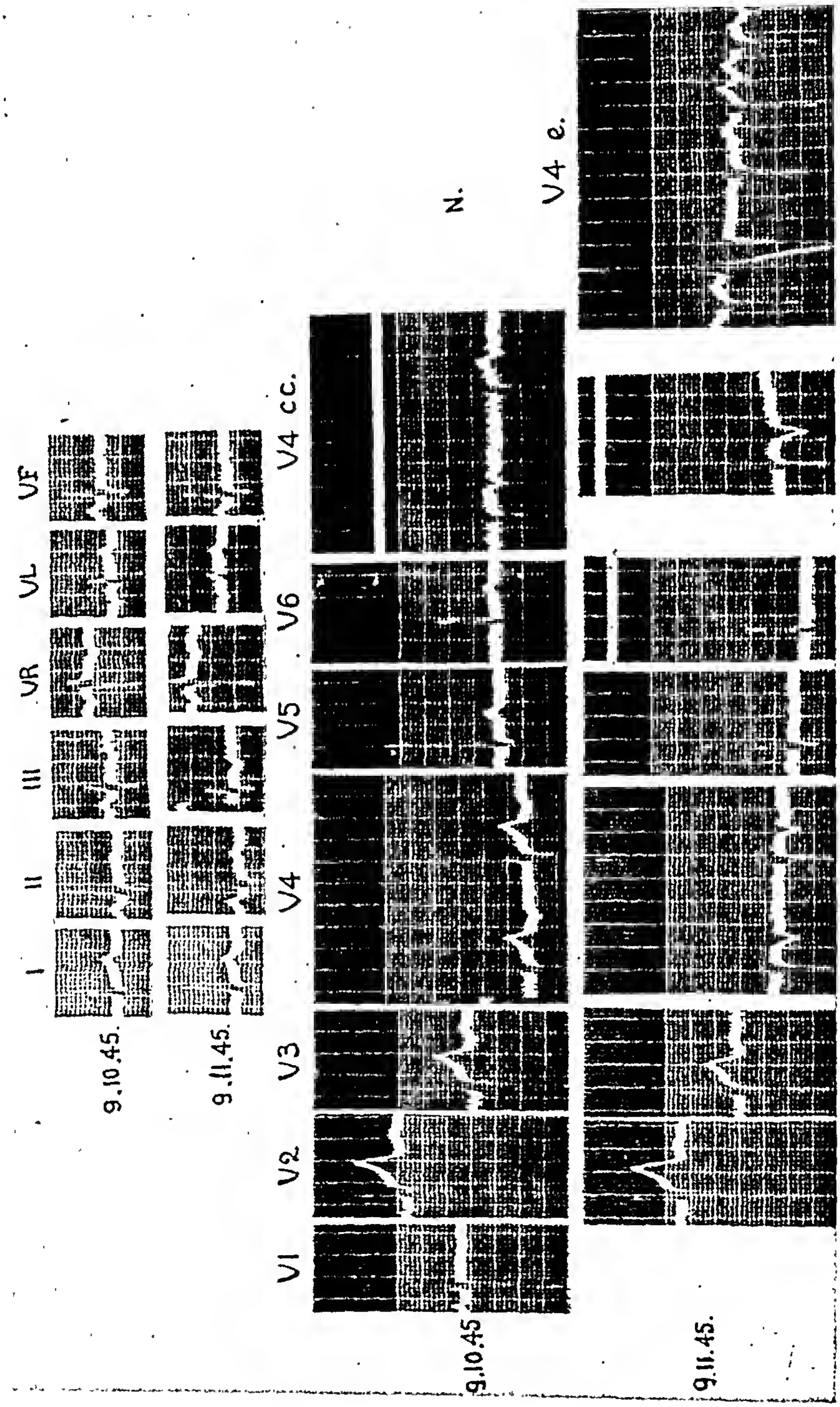

Fig. 2.—Electrocardiograms in Case 1. See text for explanation.

by the underlying condition of the heart, and even by conditions existing locally in the myocardium. In some cases in which the T waves were extremely labile, it was possible to change the polarity of this deflection at pleasure.[7]

During carotid sinus massage the T waves of some hypertensive individuals became inverted when the heart rate was relatively fast and the blood pressure was still above the normal range. In such cases the T-wave changes cannot be ascribed to abnormal variations in the heart rate or in the blood pressure. That carotid sinus stimulation can exert direct effects upon the ventricular myocardium seems improbable because all attempts hitherto have failed to demonstrate any direct action of the vagus nerves on the ventricular muscle. Sometimes the inversion of the T waves induced by massage of the carotid sinus region persisted for a considerable period and only became upright when the heart rate and the blood pressure had returned approximately to their original levels.

Frequently the inversion of the T waves produced by carotid sinus stimulation was the sole electrocardiographic abnormality detectable, but the suspicion that the heart was abnormal which it aroused was supported by the clinical data. The most striking changes in the T waves were recorded in patients with arteriosclerotic and hypertensive heart disease, but the same phenomena were occasionally observed in syphilitic, rheumatic, and congenital heart disease.[6,7]

ILLUSTRATIVE CASES

CASE 1.—The patient was a man, aged 55 years, whose blood pressure had been elevated for several years. The electrocardiograms taken on Sept. 10, 1945, were not definitely abnormal, but the contour of the T waves as atypical, particularly in Lead V_4 (Fig. 2). On carotid sinus stimulation, these atypical T waves became inverted (V_4 *c c*). On the following day the patient's clinical condition and the deflections of the limb leads were unchanged, but the T wave was inverted in Lead V_4 and flat in Leads V_5 and V_6. Carotid sinus stimulation increased the depth of the inverted T wave in Lead V_4 (V_4, *c c*), but produced no changes in the other leads. After exercise the patient complained of retrosternal oppression and the T waves in Lead V_4 became upright (V_4, *e*); at this time, however, the T waves of the complexes which followed compensatory pauses due to extrasystoles were flat or showed slight terminal inversion. All of the T waves were inverted when the effect of the exercise had worn off. Serial electrocardiograms taken at intervals over a period of one year showed striking changes in the shape of the T waves not associated with changes in the patient's clinical status.

CASE 2.—The electrocardiograms reproduced in Fig. 3 are those of a man, aged 53 years, who had hypertensive heart disease. In the records taken on Sept. 25, 1947, the T waves are flat in Lead II and slightly inverted in Lead V_F. The Q-T interval is somewhat prolonged and, following long postextrasystolic diastoles, there is flattening of this deflection in Lead I. In the tracings of the following day the T waves of precordial Leads V_5 and V_6 were somewhat atypical before and definitely inverted during carotid sinus stimulation (V_5 *c c* and V_6 *c c*); stimulation also induced moderate changes in the T deflection in Lead V_4 (V_4 *c c*).

CASE 3.—The electrocardiograms reproduced in Fig. 4 are those of a man, aged 51 years, with hypertensive heart disease. The tracing of May 5, 1946, shows left axis deviation and flat T waves in Lead II. On Jan. 14, 1947, one month after splanchnicectomy, the T waves were taller and the heart rate was faster. On Oct. 25, 1947, electrocardiograms were taken before and after carotid sinus stimulation. The classical limb leads labelled *a* were taken before and the tracings *b* during carotid sinus stimulation. The precordial leads were apparently normal, but the T waves in Leads V_4 and V_5 were atypical, and of the type that very often become inverted during carotid sinus stimulation. During carotid sinus massage the heart rate decreased,

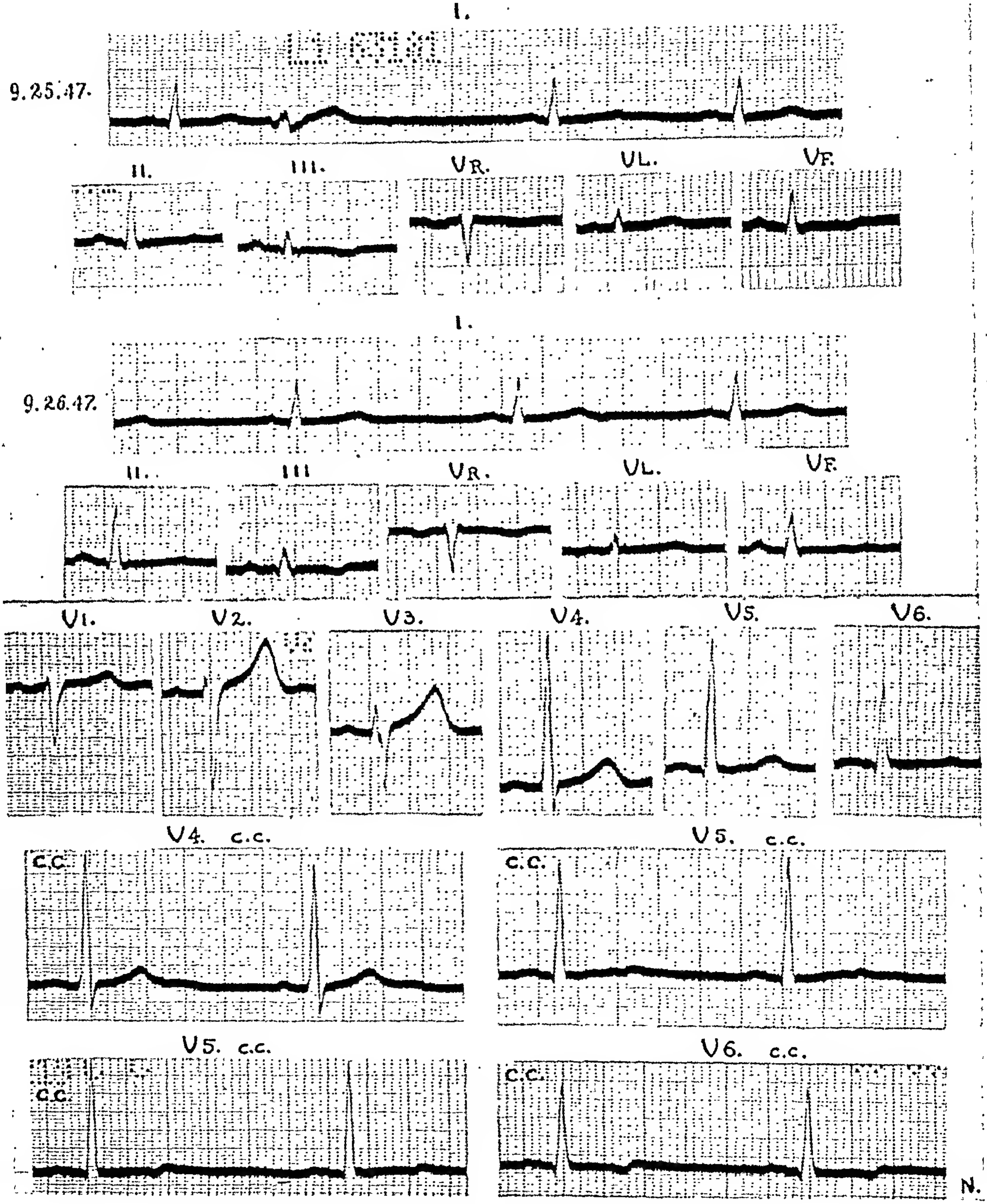

Fig. 3.—Electrocardiograms in Case 2. See text for explanation.

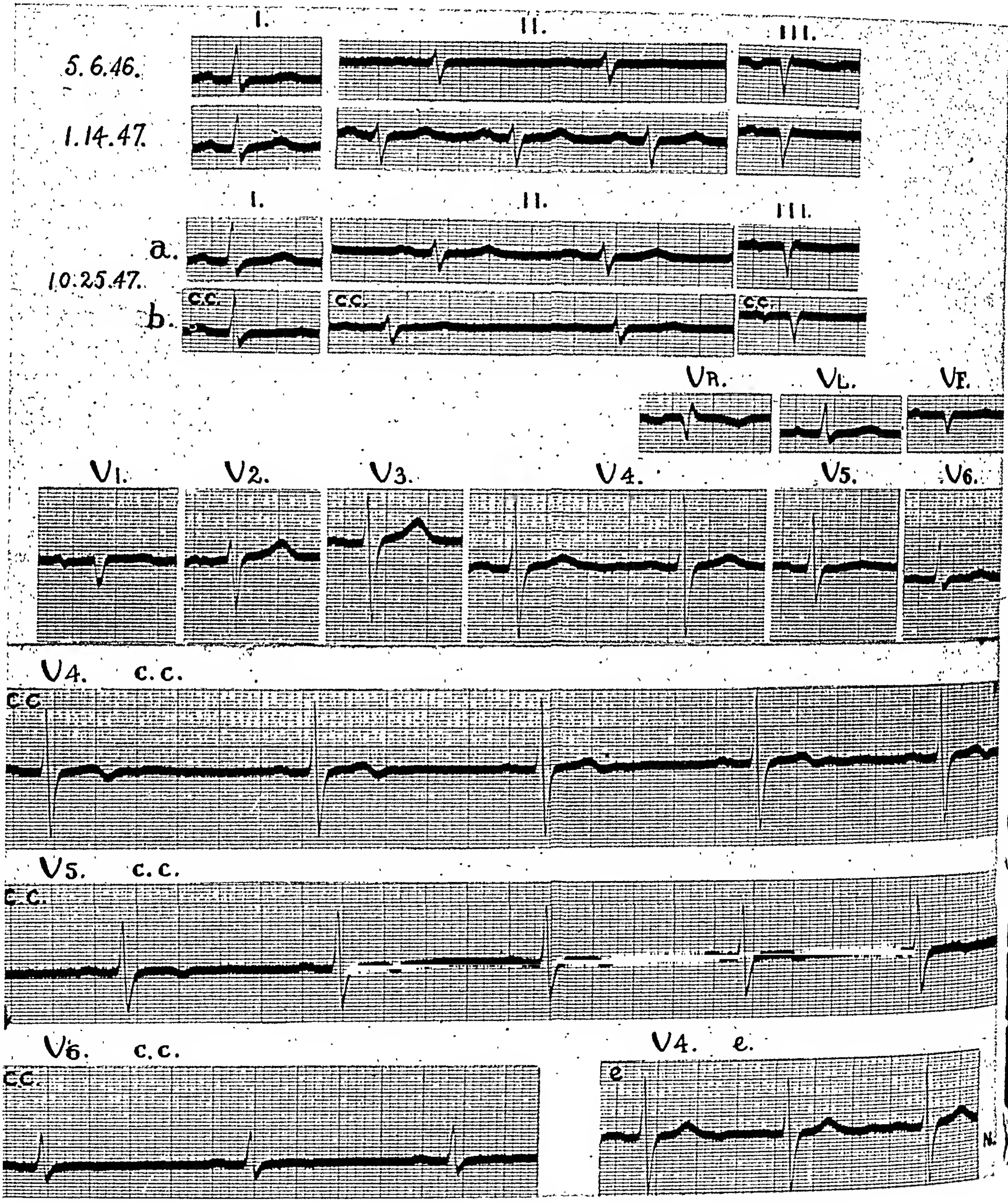

Fig. 4.—Electrocardiograms in Case 3. See text for explanation.

the blood pressure fell from 160/110 to 122/88, and the T waves became inverted in these leads (V_4cc and V_5cc). In Lead V_6 the T deflections became nearly isoelectric (V_6cc). The tracing marked V_4e was recorded after moderate exercise. Here the T waves are upright but atypical. In the electrocardiograms taken a few hours later the T waves were flat in Leads II, V_4, V_5, V_6, and V_R.

CASE 4.—The patient was a man, aged 62 years, who was having severe attacks of angina pectoris. The electrocardiograms showed inversion of the T waves which became more pronounced during carotid sinus stimulation. The complexes reproduced in Fig. 5 were selected from a continuous tracing taken during an attack of angina pectoris. During the attack the T waves became upright and there was slight downward displacement of the RS-T junction. The Q-T interval was considerably prolonged while the T wave was upright, and this deflection was definitely atypical in form. Note that it is distinctly notched and that the final limb falls very slowly. In other electrocardiograms taken on the same patient during attacks of angina pectoris, reversal of polarity of the T waves was observed with simultaneous pronounced RS-T displacement. In Lead V_R the displacement was upward and was accompanied by terminal inversion of the T wave; in Leads V_3, V_4, V_5, and V_6 the displacement was downward and the terminal part of the T wave was upright.

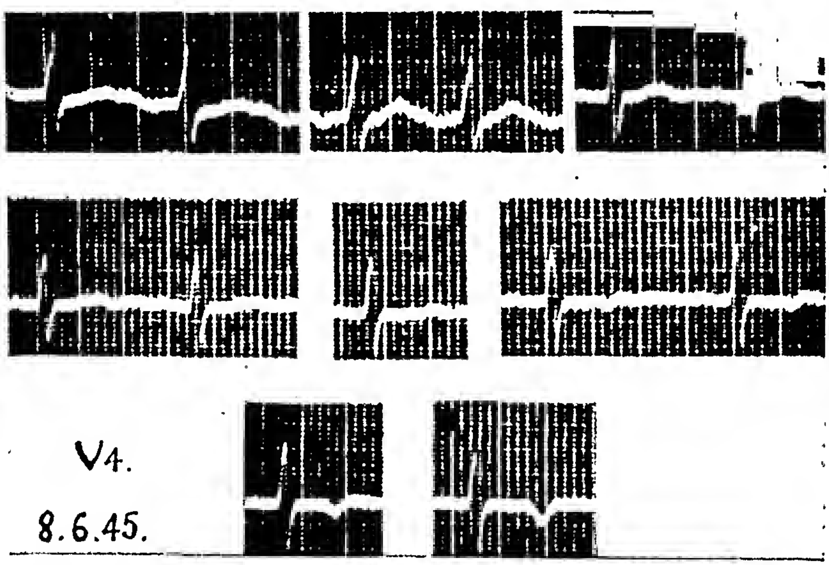

Fig. 5.—Electrocardiograms in Case 4. The complexes reproduced were selected from a continuous tracing taken during an attack of angina pectoris. During the attack the T waves became upright and these deflections were definitely atypical in form. The Q-T interval was considerably prolonged while the T deflection was upright.

CASE 5.—A 56-year-old man complained of pain in the left upper quadrant of the abdomen. The blood pressure was 190/130 and there was a history of mild angina pectoris. Electrocardiograms taken on Aug. 20 and Sept. 1, 1946, were similar to those taken on Sept. 3, 1946, which are reproduced in Fig. 6, *a*. The T waves are flat in all the limb leads and inverted in precordial Leads V_3, V_4, V_5, and V_6. Prolonged carotid sinus massage produced moderate bradycardia, and a fall in the blood pressure to 120/80 for a period of at least one-half hour. During this time the T waves became progressively more inverted in the precordial leads, the previously isoelectric deflections in Leads I, II, and III became inverted, and those of Lead V_R became upright (Fig. 6, *b*). Moderate exertion produced tachycardia, with a rise in the blood pressure to 240/140. The T waves became upright. Tracing V_3, *e* shows a series of complexes from a continuous tracing. The first strip is the control and the other strips show the progression of the changes following the exercise test. On Sept. 18, 1946, the patient felt stabbing pain in

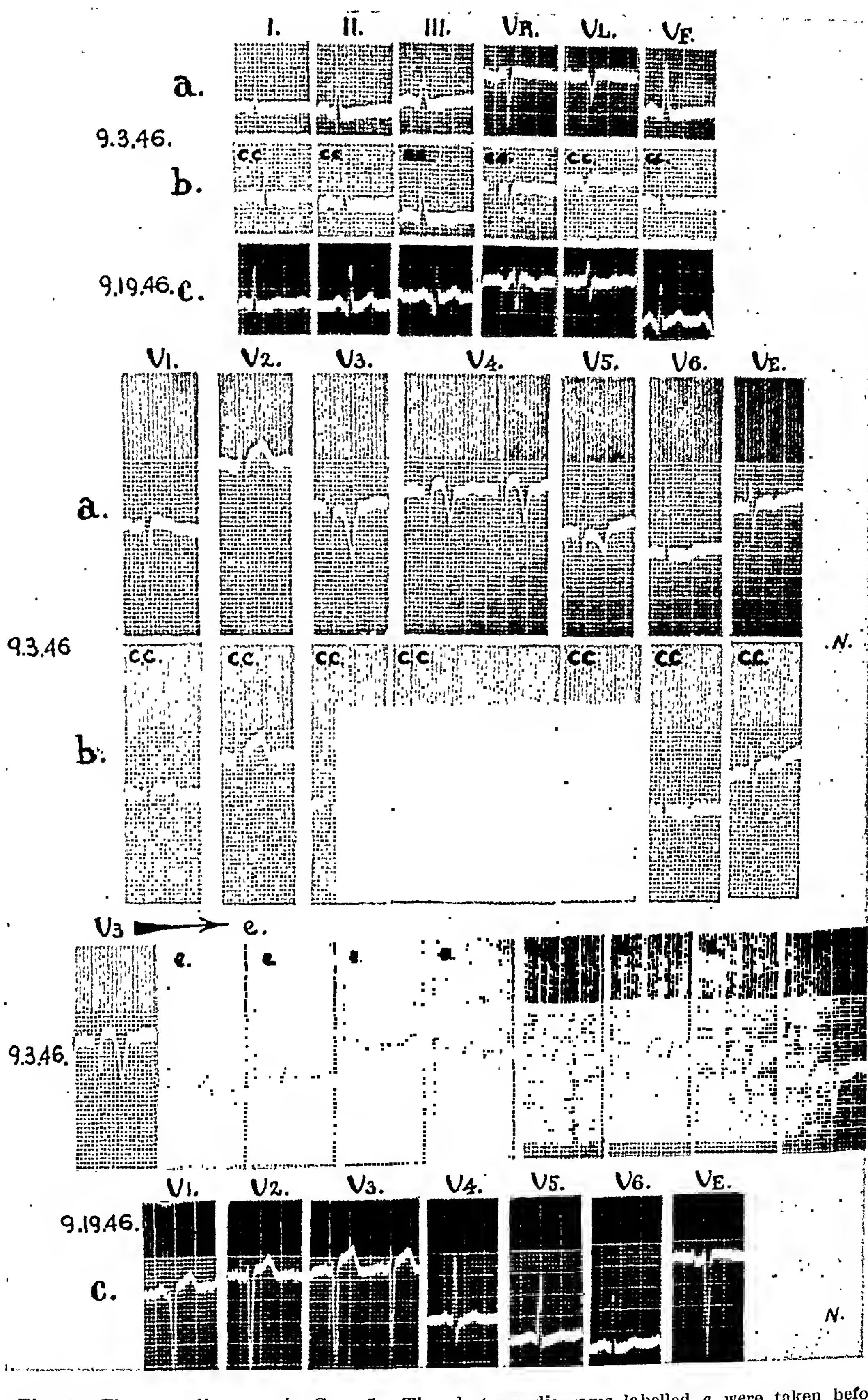

Fig. 6.—Electrocardiograms in Case 5. The electrocardiograms labelled *a* were taken before, and the tracings *b* during prolonged carotid sinus massage. Tracing V_3, *e* shows the progression of the changes following an exercise test. The electrocardiograms labelled *c* were taken several hours after an episode suggesting myocardial infarction.

the left upper quadrant with radiation to the left arm and precordium. On the following day his condition was precarious; shock was severe and the blood pressure fell to 120/75. The electrocardiograms taken at this time showed a pronounced reduction in the size of the R waves in Leads V_2 and V_3, slight upward displacement of the RS-T segment in Lead V_3, and deep Q waves in Leads II, III, and V_F. The most striking change, however, was the reversal of polarity of the T waves in all leads (Fig. 6, *c*). This pnenomenon was observed in a series of electrocardiograms taken during a one-half hour period. A fresh anteroseptal myocardial infarction was suspected. The patient died eighteen hours later. The autopsy showed general arteriosclerosis and fresh myocardial infarction. The lower part of the septum and a small area in the anterior ventricular wall were affected. The subendocardial layers and papillary muscles were predominantly involved. The necrotic process was found to be more advanced in some places than in others. The coronary arteries, chiefly the anterior descending branch of the left coronary, were partially occluded. There was, however, no complete coronary occlusion. Nearly two liters of blood were found in the left pleural cavity, the hemothorax being due to the rupture of an aneurysm of the descending aorta.

DISCUSSION

In the electrocardiograms of normal persons the contour of the T waves varies within rather narrow limits. In the tracings of patients with obvious or suspected heart disease, however, T waves of atypical shape are fairly common. Many of these atypical T deflections become inverted during carotid sinus pressure, after long postextrasystolic diastoles, or in the course of time even when there has been no definite change in the patient's clinical status. On the other hand, inverted T waves, particularly those in which the inversion is sharp and terminal, are often converted into atypical upright T waves by exertion, or other circumstances which increase the load upon the heart. The same reversal in polarity may occur during an attack of angina pectoris or even in the course of myocardial infarction. The changes in the T waves under consideration may be accompanied by changes in the level of the RS-T junction. They are not secondary to changes in the form of the QRS complex. Consequently, these T-wave changes are of the kind called primary by Wilson and Finch[8]; they depend upon changes in the ventricular gradient,[9,10] or, in other words, upon variations in the repolarization process, presumably dependent upon factors which affect the ventricular myocardium locally.

In 1931, Wilson, Macleod, and Barker[9] pointed out that in normal subjects the ventricular gradient points from the base toward the apex of the heart and suggested that this means that the average length of systole is greater in the base of the heart than at the apex, or greater on the inner than on the outer aspects of the ventricular walls, or both.

Recently a number of investigators have published electrocardiograms obtained by introducing an exploratory electrode into the cavity of the human right ventricle.[11,12,13] When the heart is normal the T waves inscribed in such leads are sharply and deeply inverted. In leads from the right side of the precordium, the QRS deflections are similar in general outline to those of the internal leads, but the T waves are strongly positive. It is evident, therefore, that although the subendocardial muscle of the right ventricle passes into the active state in advance of the subepicardial muscle, it passes out of this state later. In other words, the duration of the excited state is longer on the inner than on the outer aspect of

this wall. Whether or not this is also true of the left ventricular wall is uncertain. The T wave is normally sharply inverted in Lead V_R, which presumably reflects the potential variations of both of the ventricular cavities, and this strongly suggests that the cavity of the left ventricle, like that of the right, is negative during the inscription of this wave. It is true that Wilson and Herrmann,[14] in experiments in dogs, found that the deeper layers of the left ventricular wall pass out of the refractory period earlier than the superficial layers. In their experiments, however, the heart was exposed, and cooling and drying of the epicardial surface may have increased the duration of the excited state of the outermost layers of the muscle. There are, furthermore, no data bearing upon the form of the T deflection in direct epicardial leads or in leads from the ventricular cavities in these experiments. Byer, Ashman, and Toth[15] in experiments in dogs in which the chest was not opened have shown that cooling the endocardial surface of the heart prolongs the Q-T interval and greatly increases the size of the normally upright T waves in leads from the precordium.

We may conclude, tentatively, that the duration of the excited state is greater on the inner than on the outer surface of the ventricles, and, consequently, that the cavities of both ventricles are negative and the epicardial surfaces of both ventricles are positive during the inscription of the T deflection. If this is the case, reversal in polarity of the T wave is the result of a change in the relative length of systole on the two surfaces of the ventricular walls. No detailed explanation of this phenomenon is possible until we know what factors determine the normally greater duration of systole on the inner aspect of the ventricular walls, and how they are modified by various procedures. Some of the factors that come to mind are: blood supply, temperature, the influence of the vegetative nervous system, differences in tension in the various parts of the ventricular walls during ventricular contraction, and inherent differences in the muscle of different parts of the myocardium. There are at the present time few data bearing upon the influence or lack of influence of these factors or of others that may be involved. It has, however, been shown that local ischemia of the ventricular wall, produced by compression of a coronary artery, induces sharp inversion of the T waves in direct leads from the epicardial surface.[16] It has not been shown that the T waves of unipolar cavity leads are affected in the opposite manner, although it seems probable that this is the case. A more severe grade of ischemia leads to elevation of the RS-T segment in the epicardial leads and presumably to downward RS-T displacement in the cavity leads.

In a case of syphilitic aortitis reported elsewhere, the coronary blood flow was evidently greatly decreased. During life the patient had very frequent attacks of anginal pain. The autopsy showed that the coronary ostia were almost completely obliterated although the coronary arteries themselves were not involved. There was extensive necrosis of the subendocardial muscle of the left ventricle including that of the septum and the papillary muscles. In the right ventricular wall, patchy necrosis was present.[17] The subendocardial arteriolar plexus, described by Gross,[18] and the Thebesian vessels did not prevent necrosis, and only the Purkinje network remained undamaged.[17] These findings suggest that when the coronary circulation is uniformly impaired, lesions are likely to

occur in those places where systole is thought to be longest in normal subjects. It is probable that the physiologic, mechanical, and circulatory conditions are not entirely uniform throughout the left ventricular walls.[17,19,20] During the attacks of angina pectoris in this case, the electrocardiographic abnormalities consisted of downward displacement of the RS-T segment in the leads from the left side of the precordium and upward RS-T displacement in Lead V_R. Similar electrocardiographic changes have often been recorded during attacks of angina pectoris,[21-25] and there is some evidence that when anginal seizures are severe and persistent, necrosis of the subendocardial layers of the left ventricle is not infrequent. In 1932 Buchner[26] demonstrated that in the hearts of patients with angina pectoris necrosis was confined chiefly to the inner layers and papillary muscles of the left ventricle. Other studies have confirmed these observations, and RS-T displacement of the type described has been related to subendocardial injuries.[17,19,25,27-30]

The reversal of polarity of inverted T waves in the precordial leads during attacks of angina pectoris and the downward displacement of the RS-T segment accompanying it strongly suggest ischemia of the subendocardial muscle of the left ventricle.[19] In one case in which this phenomenon was present, necrosis affecting chiefly the subendocardial and papillary muscles of the left ventricle was observed.[19] Sodi-Pallares, Vizcaíno, Soberón, and Cabrera[12] have reported a case in which the inversion of the T wave in a lead from the right ventricular cavity became more pronounced during a spontaneous attack of angina pectoris. They ascribed this phenomenon to subendocardial ischemia.

We have shown that exertion and carotid sinus stimulation may reverse the polarity of the T waves under certain circumstances. Both have pronounced effects upon the heart, mediated at least to a large extent, through the vegetative nervous system. It is, therefore, difficult to say whether the changes in the T waves which they induce depend directly upon the changes in the heart rate and its effects upon coronary blood flow, upon the mechanics of cardiac contraction, tension in ventricular walls, and so forth, or whether these effects are primarily due to alterations in sympathetic and vagal tone. Segers[31] has shown that mechanical factors such as the tension in the cardiac walls, and chemical factors such as the concentration of adrenalin, acetylcholine, potassium, and calcium have important effects upon the monophasic electrogram of the frog's heart and particularly upon the cardiac afterpotentials.[31] We have no data which justify any conclusion as to the exact mechanism by which exertion or carotid sinus stimulation produce the electrocardiographic effects described.

SUMMARY

In normal subjects the polarity and contour of the T waves are relatively constant. Atypical T waves of normal polarity occur only occasionally in the tracings of normal subjects, but are common in the electrocardiograms of patients with heart disease.

In many instances the behavior of these atypical T waves and the previous or subsequent clinical status of the patient indicate that the myocardium is abnormal.

During carotid sinus stimulation and after long postextrasystolic diastoles, many of these atypical upright T waves become inverted. On the other hand, many inverted T waves are converted into atypical upright T waves by exertion or angina pectoris.

In some cases atypical upright T waves furnish the only objective evidence that the heart is not normal.

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CATHETERIZATION OF THE CORONARY SINUS IN MAN

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THE technique of intravenous catheterization in man[1] is invaluable for clinical and physiological studies because it enables one to measure the pressure and sample the blood in the major vessels leading from the brain, liver, kidney, or right side of the heart. Cardiac and pulmonary arterial catheterization is performed most frequently in order to diagnose congenital defects of the heart or to determine cardiac output by the direct Fick method. In the course of such studies in this laboratory the catheter tip was placed inadvertently in the coronary sinus, without ill effect, in four of a series of twenty-five consecutive patients. The purpose of this communication is to report these cases and the data obtained concerning the pressure relationships and the oxyhemoglobin saturation of the blood in the human coronary sinus.

METHODS

Intravenous catheterization was performed with a Number 9 USCI cardiac and large vein catheter,† which was inserted into a tributary of the right basilic vein and passed via the basilic, axillary, subclavian, and innominate veins and the superior vena cava into the right atrium, and from there presumably into the right ventricle. An indwelling 18 gauge needle was inserted through procainized skin into the femoral artery. Pressures were taken with Hamilton manometers,[2] while high frequency ballistocardiograms[3] and pneumograms were recorded by suitable tambours in the same optical system. After preliminary clearing of the catheter and needle of saline or sodium citrate solution by the withdrawal of ample amounts of blood, venous and arterial samples were taken in oiled syringes containing sufficient heparin solution (1 per cent) to fill the dead space in the tip. The samples were handled anaerobically and stored over mercury in a refrigerator. They were analyzed in duplicate within eight hours for content of oxygen by the technique of Van Slyke and Neill.[4] The allowable difference in duplicate analyses was 0.10 volume per cent. Hematocrit deter-

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†These catheters are manufactured in various sizes (French scale) by the United States Catheter and Instrument Corporation, Glens Falls, N. Y. Since these observations were made, No. 10 catheters have proved to be more generally satisfactory for routine cardiac, hepatic, and renal catheterization procedures in this laboratory.

minations also were made in duplicate on each sample in order to exclude errors caused by possible slight dilution of the sample withdrawn through the catheter. Any necessary small corrections were included in calculation of the venous oxyhemoglobin saturation and the arteriovenous oxygen difference.

CASE REPORTS

CASE 1.—A 52-year-old woman entered the hospital with a scabious dermatitis and mild diabetes mellitus which was controlled by dietary means alone. The cardiovascular system was essentially normal. In the course of an attempt to measure the cardiac output by the direct Fick method (Nov. 8, 1946) the catheter tip was placed in a position thought to be near the conus arteriosus of the right ventricle. However, when subsequent analysis of the three samples of blood withdrawn through the catheter revealed their oxyhemoglobin saturation to be surprisingly low and the calculated cardiac output to be absurdly small, it was suspected that the catheter tip had been elsewhere (Table I). Moreover, the photographic record of pressure changes transmitted through the catheter manifested an unfamiliar pattern (Fig. 1).

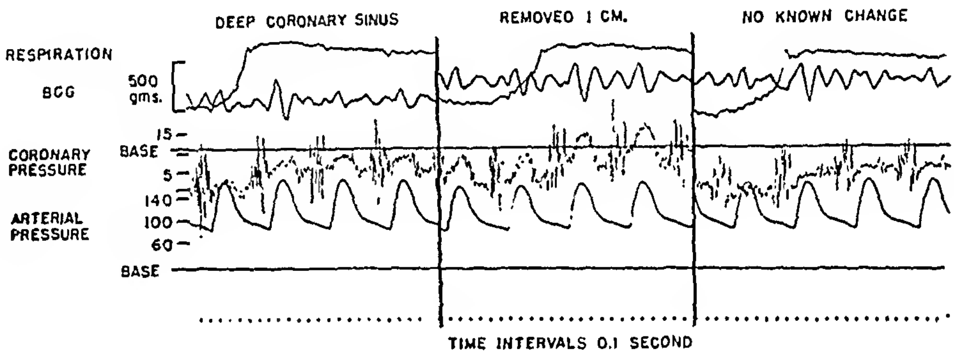

Fig. 1.—Optical records of respiration (expiration upward), ballistocardiogram, coronary venous pressure, and femoral arterial pressure in Case 1. The pressure scales are in mm. Hg (Hamilton manometers). The first record was taken with the catheter tip probably in a venous tributary of the coronary sinus. Before the second record the catheter had been withdrawn slightly. Before the third it had not been manipulated.

CASE 2.—A 25-year-old woman entered the hospital for diagnostic studies of a suspected patent ductus arteriosus. Complete cardiac catheterization was carried out (Jan. 17, 1947) and blood samples and pressure tracings were taken from the pulmonary artery, its right and left branches, the lower portion of the right ventricle, the right atrium, and the superior and inferior venae cavae (Fig. 2). To rule out the possibility of a high ventricular septal defect, the catheter tip was then advanced from the right atrium into a position supposedly in the conus arteriosus of the right ventricle, and blood was drawn for analysis. Instead of a higher oxygen content than the other ventricular, atrial, and vena caval samples, this blood showed an exceptionally low value inconsistent with the others and quite out of the normal range (Table I). On this occasion the true position of the catheter in the coronary sinus was not known during the procedure but was suspected when the blood analysis revealed the low oxygen content. Thereafter, the entrance of the catheter into the coronary sinus was recognized as it occurred during fluoroscopy.

CASE 3.—A 26-year-old man entered the hospital for study of mild essential hypertension. Three and one-half years previously he had undergone a limited bilateral lumbodorsal sympathectomy (Smithwick). At the time of this study (Feb. 4, 1947) the heart was normal in size by radiographic measurement, the electrocardiogram was interpreted as being within normal limits, and the sphygmomanometric arterial pressure was 140-155/95-110. In the course of

TABLE I. BLOOD OXYGEN AND CARDIAC OUTPUT DATA

	CASE 1 (NORMAL)	CASE 2 (PATENT DUCTUS)		CASE 3 (HYPERTENSION)	CASE 4 (PATENT DUCTUS)	
Coronary venous blood						
O_2 content, ml. per l.	60.4	38.0		87.6	42.5	
O_2Hb content, ml. per l.	60.0	37.6		87.0	42.1	
O_2Hb sat., per cent	31.4	22.6		41.1	25.8	
Arteriovenous O_2 diff., ml. per l.	123.2	117.6		116.5	112.5	
Mixed venous blood						
Source		RIGHT VENTRICLE	PULMONARY ARTERY	RIGHT VENTRICLE	RIGHT VENTRICLE	PULMONARY ARTERY
O_2 content, ml. per l.	Not obtained	113.5	130.9	161.6	100.0	111.4
O_2Hb content, ml. per l.		112.5	129.9	160.6	99.1	110.5
O_2Hb sat., per cent		67.8	78.2	76.0	60.7	67.7
Arteriovenous O_2 diff., ml. per l.		42.1	24.7	42.5	55.0	43.6
Arterial blood						
O_2 content, ml. per l.	183.6	155.6		204.1	155.0	
O_2Hb content, ml. per l.	181.2	153.2		201.7	152.6	
O_2Hb sat., per cent	95.0	92.3		95.3	93.6	
O_2Hb capacity of blood, ml. per l.	190.9	166.0		211.7	163.1	
Resp. O_2 uptake, ml. per min.	208	222		216	345	
Cardiac output, liters per min. (= resp. O_2 uptake ÷ A-V O_2 diff. of mixed venous blood)	Not determined	5.27 (Systemic circuit)	9.00 (Pulmonary circuit)	5.08	6.28 (Systemic circuit)	7.92 (Pulmonary circuit)
False cardiac output based on coronary A-V O_2 diff., liters per min.	1.69	1.89 (64.2 per cent error)		1.85 (63.6 per cent error)	3.06 (51.3 per cent error)	

a cardiac catheterization performed for the estimation of cardiac output, the tip was placed in the coronary sinus, where its position was recognized, and pressure tracings (Fig. 3) and blood samples (Table 1) were taken.

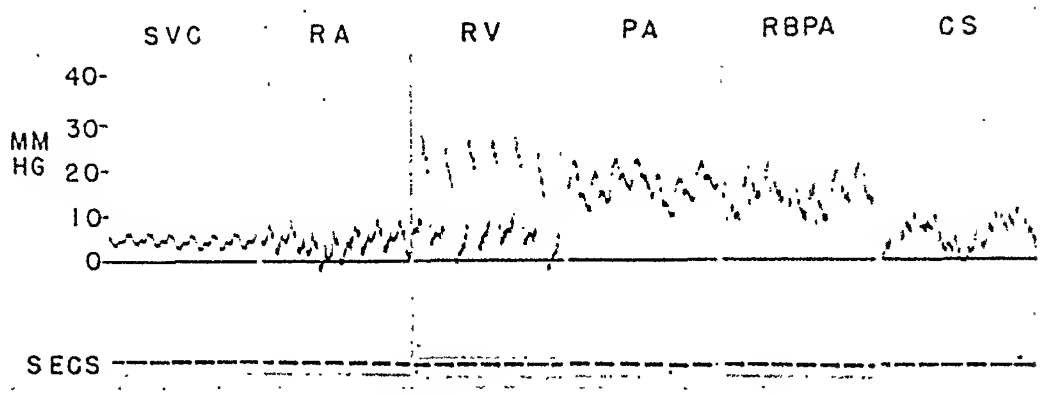

Fig. 2.—Slow optical records of pressures obtained with the catheter tip at various sites in Case 2. *SVC*, superior vena cava. *RA*, right atrium. *RV*, right ventricle. *PA*, pulmonary artery. *RBPA*, right branch of pulmonary artery. *CS*, coronary sinus. Note the mechanical disturbances produced by ventricular systole.

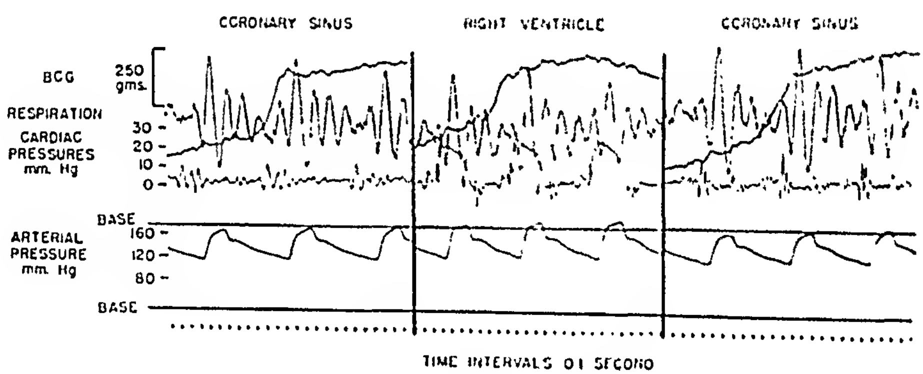

Fig. 3.—Optical records from Case 3. Coronary sinus tracings arranged for comparison with right ventricular pulse waves. Notations as in Fig. 1.

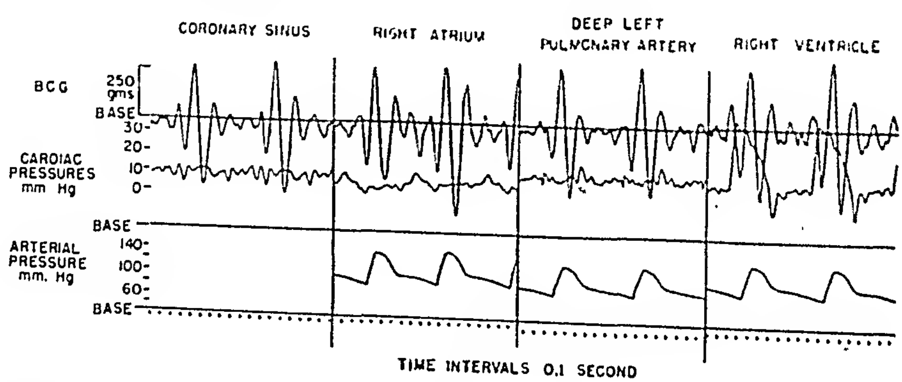

Fig. 4.—Optical records from Case 4. Coronary sinus tracing arranged for comparison with those from the right atrium and ventricle, and one taken from a small distal branch of the pulmonary artery in the left lung. Notations as in Fig. 1.

CASE 4.—A 15-year-old boy entered the hospital for diagnostic studies of congenital heart disease. The heart by x-ray study was within normal limits of size and shape except for moderate prominence of the right atrial and ventricular shadows. There was a loud systolic and a questionable early diastolic murmur over the base of the heart, and the sphygmomanometric blood pressure was 130/80. At the beginning of a diagnostic cardiac catheterization (March 7, 1947) the tip entered the coronary sinus, where pressure tracings (Fig. 4) and blood samples (Table I) were taken. During the subsequent catheter exploration, evidence was obtained indicating the presence of a patent ductus arteriosus and moderate pulmonary stenosis.

SIGNS OF CATHETERIZATION OF THE CORONARY SINUS

1. *Fluoroscopic Appearance.*—The characteristic behavior of the catheter tip under fluoroscopic visualization after entering the coronary sinus was one of the most helpful signs in determining its true position in that venous channel or one of its tributaries. In an ordinary cardiac catheterization the catheter is thrust smoothly ahead until its gently curved tip lies in the right atrium.

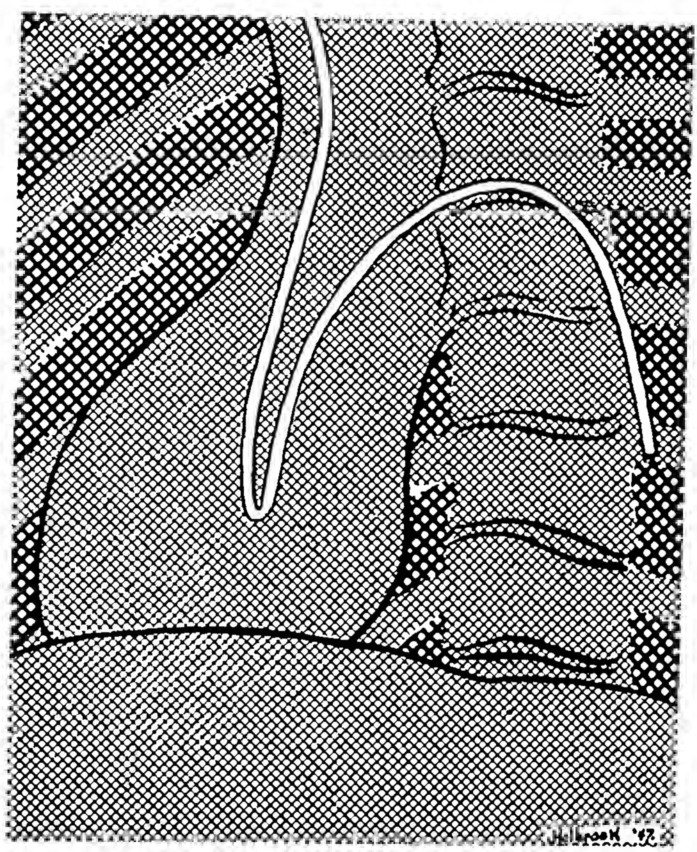

Fig. 5.—Diagram of a spot roentgenogram taken to show the left anterior oblique fluoroscopic view of the heart in Case 4 with the catheter in the left branch of the pulmonary artery. When the catheter tip was advanced farther downward and outward into the pulmonary field, highly oxygenated pulmonary "capillary" blood was obtained.

The tip then is passed toward the left and downward through the atrioventricular orifice until it reaches the diaphragmatic or apical wall of the right ventricle and is deflected upward toward the pulmonary semilunar valves. It then can be passed without resistance into the pulmonary artery (Fig. 5). By contrast,

whenever the catheter tip was passed from the atrium into the orifice of the coronary sinus, which is situated on the atrial septum just posterior to the tricuspid ostium and anterior to the rudimentary valve of the inferior vena cava, it moved immediately to the left and upward in an oblique direction along the coronary sulcus, or atrioventricular groove (Fig. 6). It encountered considerable resistance as it approached the left border of the cardiac silhouette and, if forced, failed to advance but caused the portion of the catheter within the atrium to buckle and form a loop. If it was withdrawn a few centimeters and advanced again, it followed exactly the same course repeatedly. To change its direction one had to withdraw the tip completely into the atrium and seek another route.

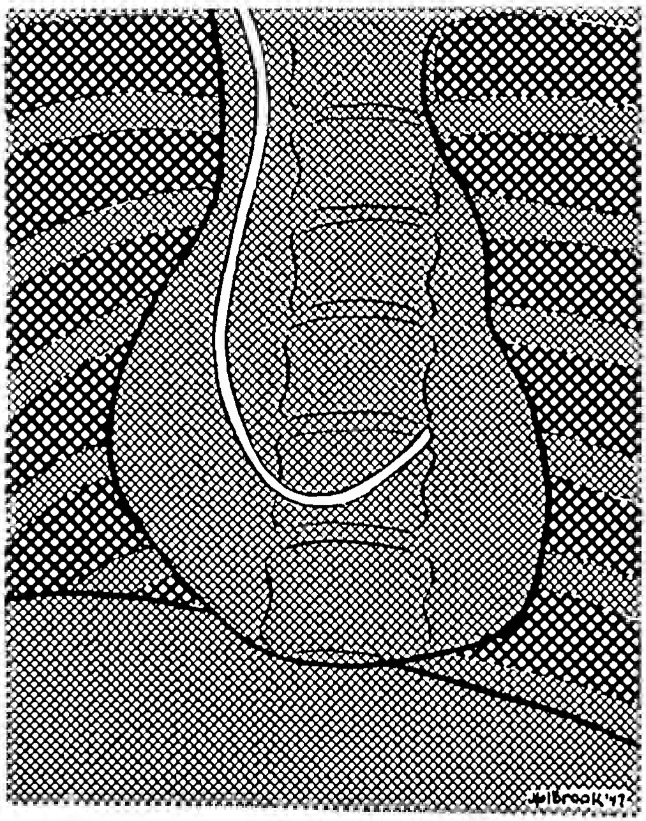

Fig. 6.—Diagram of a spot roentgenogram taken to show the posteroanterior view of the heart in Case 4 with the catheter in the coronary sinus.

2. *Oxyhemoglobin Saturation of Coronary Sinus Blood.*—The second characteristic sign of catheterization of the coronary sinus was the low oxyhemoglobin saturation of the blood obtained through the catheter. This was immediately recognizable grossly from the markedly dark color of the blood as it was withdrawn into the syringe, exceeding that obtainable from any other site in subjects at rest.

On analysis in the Van Slyke apparatus, the oxygen content of these samples of coronary venous blood was found to be extraordinarily low, while the arterio-

venous oxygen difference was correspondingly high (Table I). Thus, in the four cases here reported the oxyhemoglobin saturation of the coronary sinus blood was 31, 23, 41, and 26 per cent and the arteriovenous oxygen difference was 12.3, 11.8, 11.7, and 11.3 volumes per cent, respectively. These values are in striking contrast with the mean oxyhemoglobin saturation of 73 (standard deviation ± 4.3) per cent and the average arteriovenous oxygen difference of 4.05 (standard deviation ±0.65) volumes per cent in samples of mixed venous blood obtained in this laboratory from the pulmonary artery or right ventricle of fifty normotensive or hypertensive patients without cardiac failure and at rest (Fig. 7). The markedly greater range of the values for oxyhemoglobin saturation as compared with arteriovenous oxygen difference of the coronary venous samples in these four cases is explained by their differences in oxyhemoglobin capacity (Table I).

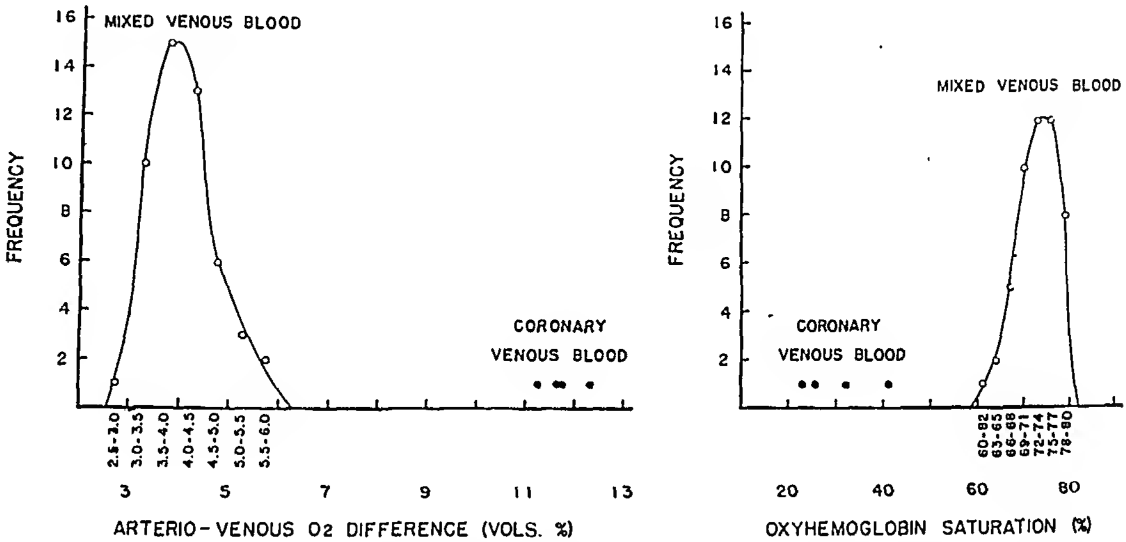

Fig. 7.—Charts illustrating comparative values and frequency distributions of the oxyhemoglobin saturation and the arteriovenous oxygen difference of coronary venous blood (in four cases) and of mixed venous systemic blood (in fifty normotensive and hypertensive subjects at rest and without cardiac failure).

3. *Blood Pressure Within the Coronary Sinus.*—The third sign which was helpful in identifying the position of the catheter tip within the coronary sinus was the character of the pressure tracings obtained with the Hamilton manometer. The pressures recorded from the sinus were usually low (0 to 15 mm. Hg) and varied rhythmically with respiration (Figs. 1 and 2). In this respect they resembled tracings obtained with the tip in the atrium, but they were dissimilar in that they ranged slightly higher and did not show the characteristic auricular pulses (Fig. 4). Instead, they usually were marked by three series of waves or vibrations, the *first* and smallest of which appeared with the atrial contraction and frequently continued to the *second* series, with ventricular contraction, while the *third* appeared with or just after the peripheral arterial pulse (Figs. 1, 3, and 4). These vibrations usually bore little resemblance to the larger, more sustained systolic pressure waves recorded from the right ventricle or the pulmonary artery. However, in Case 1 (Fig. 1), in which the catheter tip undoubtedly was advanced

farther into a coronary vein than in any of the others, there were at times definite sustained waves which at first glance did resemble those seen in tracings from the ventricle or pulmonary artery, but upon careful analysis were found to occur at the time of the third group of vibrations described earlier in this paragraph, synchronously with, or just following, the peripheral arterial (femoral) pulse waves. Hence, they occurred in the *diastolic* phase of the heart's action and therefore were considered, along with the third series of vibrations, to be possibly the result of a sudden increase in coronary blood flow early during diastole.

Thus, four types of variations were found in coronary sinus pressure: respiratory, atrial, ventricular, and "coronary." They varied in size and somewhat in shape, not only in the different subjects but also in the same subject with slight changes of position of the catheter tip within the sinus, and even from time to time without any apparent change in position (Figs. 1 and 3). Somė of these variations undoubtedly were due to greater and lesser amounts of mechanical artefacts set up in the catheter by its movement with the heart beats. Some changes, especially in the amplitude and duration of the "coronary" waves, apparently depended upon the relative completeness with which the catheter occluded the coronary sinus or a tributary vein. However, except in Case 1, the absence of well-defined, sustained wave forms resembling those obtained in the ventricle was a characteristic and helpful sign in identifying the true position of the tip when it appeared during fluoroscopy to be possibly in the pulmonary conus. The only other situation beyond the atrium where low pressures and minimal pulse waves were recorded was deep in a branch of the pulmonary artery (Fig. 4), from which a sample of blood could be seen immediately to be highly oxygenated. Moreover, this position was easily identifiable by an anterior oblique fluoroscopic view and occasioned no difficulty during catheterization (Fig. 5). This source of oxygen-saturated pulmonary "capillary" blood has been noted and described by Dexter and associates.[5]

DISCUSSION

Sosman and Dexter[6] have recognized accidental catheterization of the coronary venous system in two cases and in one of them reported the pressure to be 12 mm. Hg, the oxygen content of the blood, 7.4 volumes per cent, and its saturation, 25 per cent. These values are within the ranges of the observations here reported in four additional cases. In both groups the relative ease and apparent harmlessness of catheterization of the human coronary sinus has suggested its applicability for a wide variety of possible studies on coronary blood flow and cardiac metabolism in man. There seems little doubt that if the coronary sinus can be entered fortuitously in 16 per cent of cases, it can be catheterized deliberately in a majority of cases.*

From these observations one can state, furthermore, that in a subject at rest the degree of oxygen extraction by the myocardium from coronary blood is remarkably near complete. It follows that any considerable increase in demand by the myocardium for oxygen under conditions of exercise must be met by

*Since the presentation of this paper such studies have been undertaken elsewhere.[7,8,9]

increased coronary blood flow rather than by increased oxygen extraction. These findings in man are consistent with those reported previously by others[10,11] for the dog. Moreover, it would seem that attempts to increase the oxygen extraction by means of certain enzymic preparations are relatively unpromising. However, the technique of coronary sinus catheterization should be applicable to the solution of this problem.*

The results of this study have emphasized a major source of error in sampling mixed venous blood, as required for the determination of cardiac output by the direct Fick method. If the tip of the catheter is placed in the coronary sinus but presumed to be in the right ventricle and the oxygen content of the blood withdrawn therefrom is used in calculating the cardiac output, the resulting values are greatly in error, being less than one-half the actual cardiac output (Table I). Even if the tip of the catheter is within the atrial chamber but near the coronary orifice or in the stream of blood issuing from it, an admixture of coronary venous blood with the atrial sample may occur. In order to be certain of obtaining thoroughly mixed systemic venous blood, one should place the tip of the catheter in the pulmonary artery or the proximal portion of its right or left branch. Another distinct advantage of this practice is that it enables one to withdraw the blood in a smooth, continuous stream because of the well-sustained pulmonary arterial diastolic pressure. In the right ventricle, where the diastolic pressure approaches or falls to zero, sampling is sometimes difficult (Figs. 2, 3, and 4).

As yet, insufficient data have been collected concerning the pressure relationships in various portions of the coronary venous system. It appears that in the sinus itself the pressures are relatively low, reflecting its continuity with the atrium, and are characterized usually by minor variations due to respiratory and cardiac movements. Farther out in the system, however, there may occur in early diastole sustained waves which possibly reflect the increase in coronary blood flow at that time. It will be of interest to follow the further accumulation of data on these points.

SUMMARY

An intravenous catheter was introduced inadvertently into the coronary sinuses of four patients in the course of a series of twenty-five cardiac catheterization studies (a frequency of 16 per cent). Samples of coronary venous blood were taken for oxygen analysis, and pressure tracings were obtained with a Hamilton manometer. These cases are reported and criteria for identifying this catheter position are presented.

Oxyhemoglobin saturation values were found to be strikingly low (average, 30 per cent in four cases) as compared with control values for mixed venous blood (average, 73 per cent in fifty subjects). Coronary venous pressure levels (0 to 15 mm. Hg) and wave patterns are described. Physiologic implications of the findings and potential applications of the technique are cited.

*As this paper was being submitted for publication, a preliminary report appeared[12] indicating that in dogs breathing low oxygen mixtures the intravenous injection of cytochrome C did not increase the removal of oxygen from the coronary blood.

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A SIMPLE BIPOLAR TECHNIQUE FOR THE ANALYSIS OF THE VECTOR RELATIONSHIP BETWEEN THE UNIPOLAR AND STANDARD ELECTROCARDIOGRAPHIC LEADS

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IN 1934 Wilson[1] suggested the use of an indifferent electrode of zero potential which would make it possible to determine the potential variations at a single point on the surface of the body without reference to changes in potential at any other point. Goldberger[2] in 1942 demonstrated that electrocardiograms of similar wave form, but larger by one-half than Wilson's, could be obtained by means of an indifferent electrode consisting of two electrodes connected to a common terminal attached to the extremities not being "explored" and eliminating Wilson's 5,000 ohm resistors.

It is the purpose of this paper to demonstrate that electrocardiograms of wave form similar to the unipolar electrocardiograms can be obtained by simple bipolar leads and that this establishes the vector relationship between the unipolar and standard leads.

METHOD

The following method of taking electrocardiograms was used. The positive or "exploring" electrode was placed on the left arm and the negative or indifferent electrode at a point in the midaxillary line halfway between the apex of the right axilla and the symphysis pubis. The distance from the apex of the axilla to the pubis was measured with a tape, the distance halved, and with the end of the tape in the axilla, the other end of the tape was swung laterally so that it came to lie along the midaxillary line, its midpoint being "diametrically" opposite the extremity being "explored." A tracing was obtained which was similar in form to the unipolar left arm leads but which was twice as large as Wilson's and one-third again as large as Goldberger's. For convenience of designation, this lead was called W_L. Lead W_R is written in a similar manner, the "exploring" electrode being placed on the right arm and the negative electrode at the halfway point in the left midaxillary line. Lead W_F is obtained by the positive electrode being placed on the left leg and the negative electrode on the submental fat pad.

The bipolar electrocardiograms designated as "W" leads (Fig. 1) are presented for comparison with the augmented unipolar limb leads. The first is from a normal individual and the second from an individual who had an old anterior wall infarction.

From the Medical Unit, New York Regional Office Clinic, Veterans Administration.
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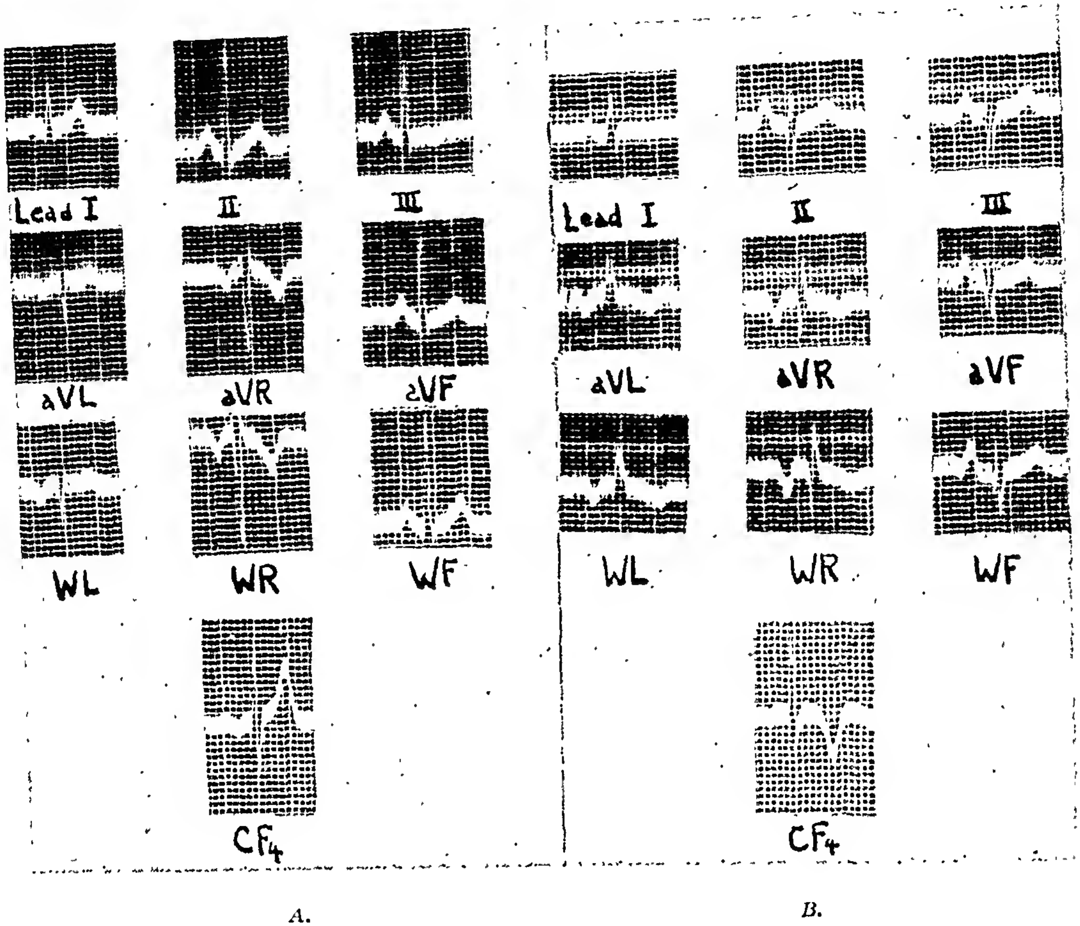

Fig. 1. Electrocardiograms showing the similarity in wave form between the augmented unipolar leads and the W or bipolar unipolar-type leads. *A*, Normal; *B*, old anterior wall infarction.

DISCUSSION

This method is not recommended for clinical use since it is based on the assumption that the heart is centrally situated and that the point midway between axilla and pubis is diametrically opposite the "explored" extremity. However, in an emergency, by the simple expedient of standardizing the electrocardiograph so that 1.0 mv. is equivalent to 0.5 cm., a reasonable facsimile of Wilson's leads can be obtained using a single pair of electrodes.

The following solution is offered. If for theoretical considerations the body is considered as an ovoid with an electrical dipole near its center which is surrounded by a uniformly conducting medium, then the potential V_L measured by an electrode at any point L on its surface, can be described by the equation $V_L = \frac{K \, Cos \, \theta}{r_1^2}$, where K is a constant and r_1 is the distance between the electrode and the center of the dipole and θ represents the angle between a line drawn from the center of the dipole and the electrode at L and a line drawn in the direction of the electrical axis of the dipole.[3] (See Fig. 2.)

The potential at W can be described by the equation $V_W = \dfrac{K \ Cos \ (180 - \theta)}{r_2^2}$ where r_2 is the distance from the center of the dipole and a point W which is diametrically opposite L.

$$\text{Then} \quad V_L - V_W = \frac{K \ Cos \ \theta}{r_1^2} - \frac{K \ Cos \ (180 - \theta)}{r_2^2}$$

$$\text{Since} \quad \frac{K \ Cos \ (180 - \theta)}{r_2^2} = -\frac{K \ Cos \ \theta}{r_2^2}$$

$$\text{Then} \quad V_L - V_W = \frac{K \ Cos \ \theta}{r_1^2} + \frac{K \ Cos \ \theta}{r_2^2}$$

$$= \frac{K \ Cos \ \theta}{r_1^2}\left(1 + \frac{r_1^2}{r_2^2}\right)$$

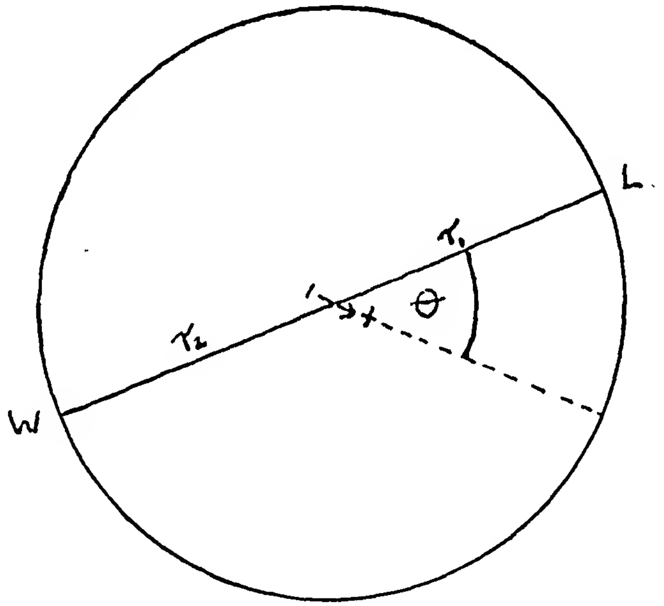

Fig. 2. The mathematical relationship between diametrically opposed electrodes and the electrical axis of the heart.

This formula is applicable to any figure which has central symmetry. For a sphere, $r_1 = r_2$ for every point L,

$$\text{Therefore} \quad V_L - V_W = \frac{2 \ K \ Cos \ \theta}{r^2}$$

Since the difference in potential at L and an indifferent electrode of zero potential T may be described:

$$V_L - V_T = \frac{K \ Cos \ \theta}{r^2}$$

then

$$V_L - V_W = 2 \ (V_L - V_T)$$

Also for a sphere, since $r_1 = r_2$, then $V_L = - V_W$

Expressed qualitatively, this is equivalent to saying that whereas Wilson derives the potential at a single extremity by the use of an indifferent electrode of zero potential, by the method described by the authors the potential variation at a single extremity may be written by tapping the potential at that extremity and its simultaneous equal and opposite variation. For example, if by Wilson's method a potential of 4.0 mv. be obtained, then by the method described by the authors one would obtain a deflection equivalent to 8.0 mv., since $V_L - V_W = 4 - (-4)$ or 8, and the wave form of the electrocardiograms must be the same although varying in amplitude by twice. (See Fig. 3.)

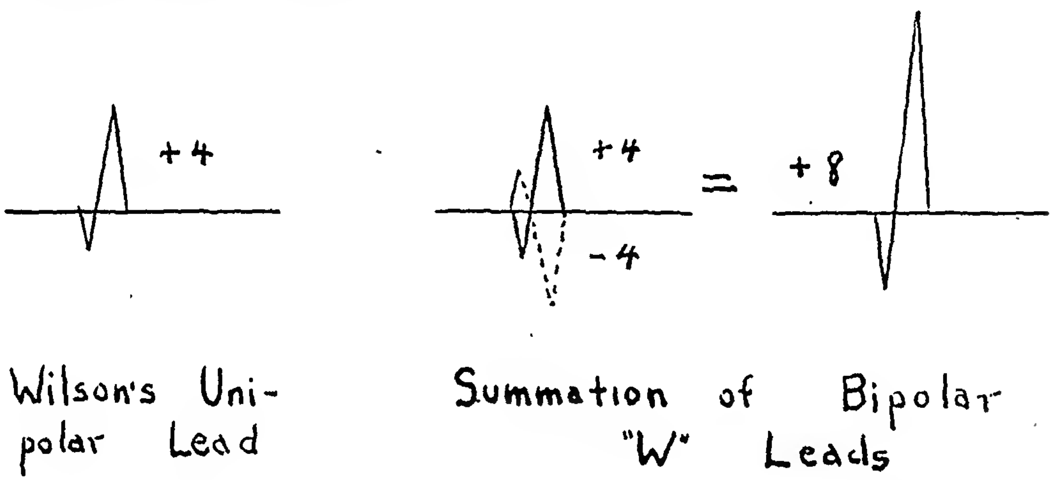

Fig. 3.—Diagrammatic representation of the summation of mirror image waves of similar form and opposite sign in bipolar unipolar-type W leads.

It is suggested that the Goldberger augmented unipolar limb leads are unipolar in the sense that the wave inscribed has similar form to Wilson's, but they actually do not employ an indifferent electrode of zero potential but rather one which measures a simultaneous quantity of opposite sign, one-half the magnitude of the Wilson unipolar lead, the summation of which gives a wave of similar form three-halves the magnitude of Wilson's. This is apparent from Goldberger's[4] explanation for the augmentation of his *unipolar* leads in which he indicates that the augmented unipolar limb leads actually represent the difference in potential between the unipolar potential of the right arm, for example, and the mean potential of the other extremities, or:

$$\text{Augmented potential of right arm} = RA - \frac{LA + LL}{2}$$

$$\text{Since} \quad RA + LA + LL = 0$$

$$\text{and} \quad LA + LL = -RA$$

$$\text{then} \quad \frac{LA + LL}{2} = -\frac{RA}{2}$$

$$\text{or augmented potential of right arm} = RA - \left(-\frac{RA}{2}\right) = 3/2\,RA$$

If the mean potential of the other extremities, $\frac{LA + LL}{2}$, is equal to one-half the potential at the right arm, $-\frac{RA}{2}$, it cannot at the same time be equal to zero (see Fig. 4.).

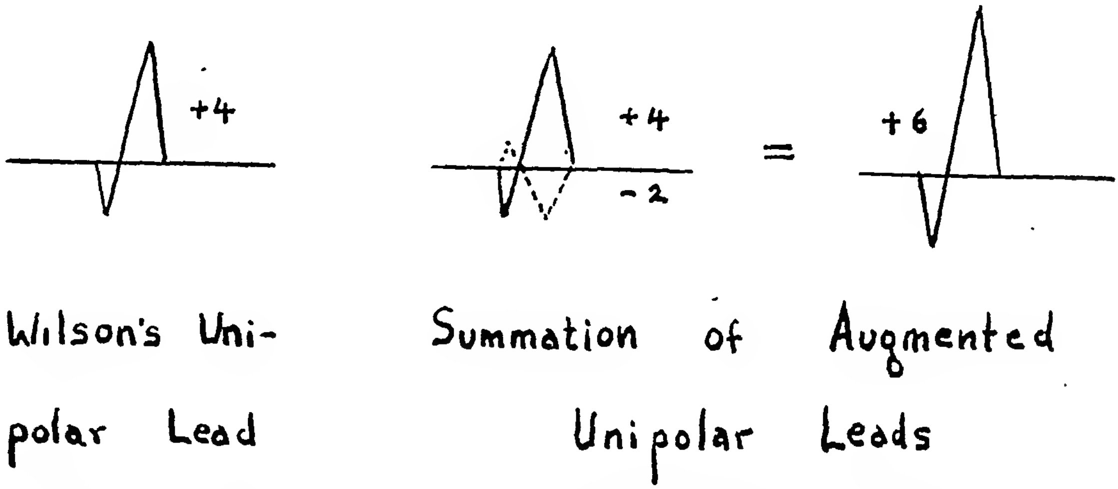

Fig. 4.—Summation of positive deflection and its half-sized negative counterpart of similar form resulting in the augmented unipolar lead.

The importance of W leads is that they demonstrate that waves similar to the unipolar leads can be obtained by bipolar leads, indicating that the unipolar leads, both Wilson's and Goldberger's, represent the resolution of vectors having the same direction as the W leads. Therefore, the unipolar leads not only "resemble" the standard leads but may be thought of as being related to the standard leads by rotation of the "indifferent" or negative electrode through an arc of 30°. The unipolar leads, therefore, as much represent the vectors passing through the heart as the standard leads represent forces passing tangentially to the heart (Fig. 5).

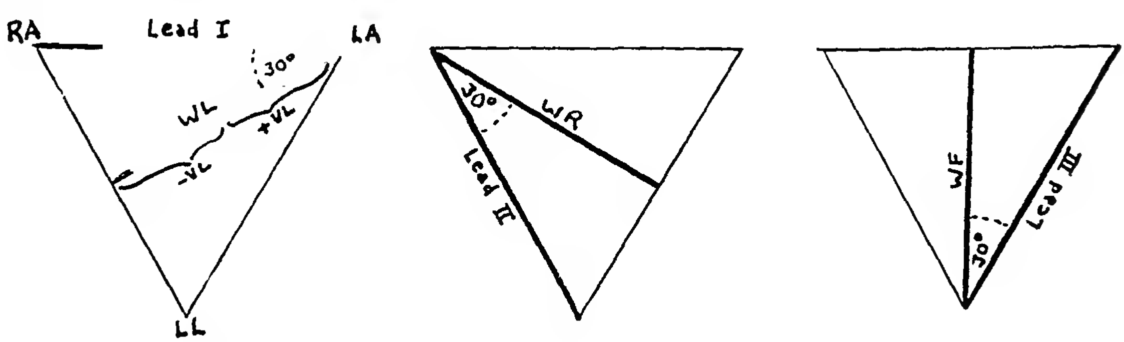

Fig. 5.—The vector relationships of the standard and unipolar limb leads.

It is of interest that the method of bipolar unipolar-type leads is not subject to the limitation of assuming that the electrical axis of the heart lies in the plane of Einthoven's triangle. In the above derivation, orientation of the axis of the heart is immaterial so long as points opposite are employed. This may have

particular significance in elucidating some of the minor discrepancies in the precordial unipolar tracings in bundle branch block.[5]

The experiment with bipolar diametrically opposed leads was independently conceived by the authors but clearly anticipated by Wilson[6] in a recent article in which he states, "If the cardiac field at points far distant from the heart is nearly equivalent to that of a doublet, leads from two points equidistant from this organ and at opposite ends of a line which passes through its center should yield complexes exactly opposite in character if the leads employed are unipolar."

SUMMARY

1. A method of obtaining unipolar-type leads with simple bipolar diametrically opposed electrodes is presented.

2. The unipolar leads may be considered as radius vectors related to the standard leads through an arc of 30°.

The authors wish to express appreciation to Dr. Morris Lattman, Chief, Cardiac Clinic, New York Regional Office Clinic, Veterans Administration, to Dr. Milton Mendlowitz, and to Mr. Walter A. Brecher for helpful suggestions and technical assistance.

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Clinical Reports

OBSTRUCTIONS OF THE SUPERIOR VENA CAVA

A Review of the Literature With Two Case Reports

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THE clinical picture of obstruction of the superior vena cava is a symptom complex and not a specific disease entity. Many papers, case reports, and discussions of various aspects of obstruction of the superior vena cava have appeared in medical literature over a period of many years, but it is difficult to find a brief summary of well-established criteria for diagnosis, prognosis, and therapy.

The purpose of this present paper is threefold: (1) to review the essential points of the literature since 1934; (2) to report two additional cases of obstruction of the superior vena cava, one of particular interest; and (3) to summarize in one place the major points of diagnosis and treatment as related to this unusual syndrome.

REVIEW OF THE LITERATURE

In 1934 Ehrlich, Ballon, and Graham[1] published a detailed review of the literature up to that time, a total of 309 cases.

Some general observations can be made regarding signs and symptoms. When obstruction of the superior vena cava has occurred, the symptoms and findings are essentially alike, regardless of the etiology. The clinical picture of obstruction is usually preceded by or accompanied by other signs and symptoms related to the factor causing the caval obstruction (bronchogenic carcinoma, for example), except when the etiological factor happens to be an intraluminal obstruction (primary thrombus) or a long-standing, otherwise asymptomatic fibrotic process in the mediastinum. In general, then, the early symptoms of cases of obstruction of the superior vena cava will be those of the causative disease concerned. Later in this paper the signs and symptoms of obstruction of the superior vena cava will be described in sufficient detail to facilitate the adequate diagnosis of this condition.

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A review of the literature from April, 1934, to Jan. 1, 1947, revea;ch surround 125 reported cases which present unquestionably the clinical syndrome o cava was tion of the superior vena cava. Several case reports have appeared which nosis.[48] included in this review because the clinical descriptions were inadequate no- support a diagnosis of complete obstruction of the superior vena cava. Hussey reported fifty-two cases of venous compression in the mediastinum with venous pressure studies. Hussey's paper was a study of venous pressure dynamics in various lesions affecting the innominate and subclavian vessels as well as the superior vena cava. The majority of these cases were not described in sufficient detail to make it possible to classify them in this study; consequently, they were excluded. Pilcher and Overholt[3] reported fifty cases of venous obstruction in the upper mediastinum. A large number of these were attributed to intrathoracic goiter. The diagnoses were based chiefly on elevated venous pressures in the upper extremities, frequently below 200 mm. H_2O, while the classical clinical picture of obstruction of the superior vena cava was not described clearly in most of the instances. Therefore, only a small percentage of these cases were included. Three foreign papers with a total of five cases were not available for this study.

The 125 cases which have been collected are classified on the basis of their etiology as follows: (1) carcinoma of the bronchus with metastasis to the mediastinal nodes, twenty cases (16 per cent)[4-10]; (2) metastatic carcinoma other than bronchogenic, nine cases (7.2 per cent)[4,5,11,12]; (3) lymphoblastomas (including Hodgkin's disease), fifteen cases (12 per cent)[4,5,11,13,14]; (4) primary mediastinal tumors, four cases (3.2 per cent)[4,15]; (5) aortic aneurysms (almost all syphilitic), twenty-nine cases (23.2 per cent)[4,5,6,11,14,16-28]; (6) mediastinitis, five cases (4 per cent)[14,29,30]; (7) "mediastinal fibrosis" (chronic mediastinitis of undetermined type with scar tissue formation, constricting bands, and other similar changes, eleven cases (8.8 per cent)[4,31,32,33]; (8) thrombosis (excluding those secondary to invasion by malignant tumors), seventeen cases (13.6 per cent)[34-46] (eight of these cases were considered to be idiopathic or primary thrombosis); and (9) miscellaneous causes, fifteen cases (12 per cent)[4,5,47,48,49] (see Table I).

Numerous instances of thrombosis of the superior vena cava are on record in which the thrombotic process was the direct result of invasion of the vein proper by malignant tumor tissue. Seventeen patients (13.6 per cent) of this group had thrombosis from other factors; since these cases are quite rare, they should be noted in some detail. In eight of the seventeen cases thrombosis was apparently primary. In the other nine cases thrombosis was thought to be secondary: in three cases thrombosis was associated with pulmonary tuberculosis; in two, with septicemia; in two thrombosis was alleged to be due to thrombophlebitis; in one it was attributed to nicotine sensitivity; and in one thrombosis was secondary to right auricular thrombosis following Bernheim's syndrome.[42] The incidence of thrombosis of the superior vena cava here recorded is considerably greater than that reported by Ehrlich, Ballon, and Graham[1] in 1934. A detailed study of thrombosis of the superior vena cava alone was published by Ochsner and Dixon in 1936.[34]

.OLOGY OF OBSTRUCTION OF SUPERIOR VENA CAVA IN 125 CASES REPORTED IN THE LITERATURE BETWEEN APRIL, 1934, and JANUARY, 1947

CAUSE	CASES	PER CENT OF TOTAL
I Carcinoma of the bronchus (bronchogenic) *with* mediastinal metastasis	20	16
II Lymphoblastomas (including Hodgkin's disease)	15	12
III Aortic aneurysm (syphilitic)	29	23.2 (total)
(a) Due to *pressure* from aneurysm 14 cases (11.2%)		
(b) Rupture into superior vena cava[5,17-27] 14 cases (11.2%)		
(c) Dissecting aneurysm (arteriosclerotic)[28] 1 case (0.8%)		
IV Metastatic carcinoma to mediastinum (excluding bronchogenic)	9	7.2 (total)
(a) Carcinoma of thyroid 4 cases (3.2%)		
(b) Others from various sources		
V Primary mediastinal tumors (two of these were considered to be malignant tumors)	4	3.2
VI Mediastinitis	5	4 (total)
(a) Tuberculosis 2 cases (1.6%)		
(b) Syphilitic 2 cases (1.6%)		
(c) Pyogenic 1 case (0.8%)		
VII "Mediastinal fibrosis"	11	8.8
VIII Thrombosis of superior vena cava (excluding those cases due to invasion of the vein by malignant tumors)	17	13.6
IX Miscellaneous causes	15	12.0 (total)
(a) Undetermined (so classified by those who reported them)		
1. Mediastinal mass present 4 cases (3.2%)		
2. No medistinal mass 4 cases (3.2%)		
(b) Acute leucemia (lymphocytic) 3 cases (2.4%)		
(c) Pericardial constriction (pericarditis) 2 cases (1.6%)		
(d) Pneumothorax (2-month-old infant) 1 case (0.8%)		
(e) Mitral stenosis—left auricular dilitation and superior vena caval compression 1 case (0.8%)		
	125 (Total)	100 (Total)

Among the group of cases under the heading of miscellaneous causes are several of special note. Three cases of obstruction of the superior vena cava have been reported in patients having leucemia. In two of these the obstruction of the superior vena cava was an incidental finding, while in one instance it was the first manifestation of leucemia to be found. This may represent a sarcoma-

tous phase of leucemia involving the mediastinal lymph nodes which surround the superior vena vava. One case of obstruction of the superior vena cava was due to pressure from a greatly dilated left atrium resulting from mitral stenosis.[48] Another unusual situation was that of obstruction due to a spontaneous pneumothorax in a 2-month-old infant.[49]

Aortic aneurysm in its various forms caused obstruction in 23.2 per cent of the cases in this collected series, as compared with 36 per cent in that of Ehrlich, Ballon, and Graham.[1] This is especially interesting in view of the fact that these authors did not include cases due to rupture of the aneurysm into the superior vena cava; this group comprised 11.2 per cent of the total cases in this present series. A complete review of spontaneous thoracic arteriovenous aneurysms reported up to 1938 has been made by Armstrong, Coggin, and Hendrickson.[17]

The incidence of primary malignant thoracic tumors as causative agents is also somewhat higher in the report of Ehrlich, Ballon, and Graham.[1] The group of cases in which obstruction is attributed to "mediastinal fibrosis," including scar tissue, chronic mediastinitis, and other allied disorders, is approximately the same in each series. It is of interest to note that benign goiter practically never causes well-developed obstruction of the superior vena cava.

DIAGNOSIS, TREATMENT, AND PROGNOSIS

The diagnostic clinical criteria of obstruction of the superior vena cava may be outlined as follows:

1. The demonstration of significantly elevated venous pressure (180 mm. H_2O or above) in the upper half of the body in the presence of normal venous pressure in the lower half of the body. This may be determined by the use of the usual venous pressure apparatus or by the observation of unquestionable edema of the upper half of the body with none in the lower extremities.

2. The demonstration of collateral circulation which circumvents the superior vena cava. This includes the observation of visibly dilated veins over the upper half of the body, chiefly the anterior chest. The use of infrared photography frequently outlines this collateral circulation. It may be visualized even better by phlebography.

3. The demonstration by phlebography of the point of obstruction or the demonstration by a roentgenogram of a mass or other lesion which might be considered adequate to cause obstruction of the superior vena cava.

The diagnosis must rest upon objective and not subjective evidence. Any symptom related to the cardiorespiratory system may be experienced by these patients. Cyanosis or deep flushing of the face is frequently seen and patients often complain of a feeling of fullness or congestion in the head and neck, especially after reclining or after stooping.

In the case of rupture of aortic aneurysms into the superior vena cava, the picture is that of acute obstruction. The signs are severe cyanosis, edema, dyspnea, and greatly elevated venous pressure in the upper extremities. Other less diagnostic findings are discussed carefully by Armstrong, Coggin, and Hendrickson.[17]

One author[14] emphasizes that the presence of a disassociation between the venous pressure and the circulation time (arm to tongue) is an important sign in obstruction of the superior vena cava. However, in most reported cases in which both are mentioned, the circulation time was prolonged.

The treatment in obstructions of the superior vena cava must necessarily be directed chiefly to the underlying disease entity. In the lymphomas, for example, radiation therapy is frequently of great help. Under roentgen radiation many large mediastinal masses will melt away, giving at least transitory relief of the venous obstructive symptoms.

In most instances patients with syphilitic mediastinitis should receive antisyphilitic therapy. Pyogenic mediastinitis demands chemotherapy or the use of antibiotics. The use of anticoagulants would be indicated in thrombosis of recent origin; no patients having anticoagulant therapy were found in this review.

There are several instances in which surgical intervention is indicated: (1) rarely, to attempt to remove benign mediastinal tumors; (2) to release fibrous bands and adhesions causing obstruction of the superior vena cava; and (3) to decompress the mediastinum in cases of marked obstruction or when the obstruction is increasing rapidly. This is frequently applicable as a temporary lifesaving procedure even when the obstruction is due to malignant tumors.

The prognosis is that of the underlying disease to a large extent. The veins adapt quite well to the obstructive process if the obstruction develops slowly. It has been noted that if the obstruction has occurred below the level of the entry of the azygos vein into the superior vena cava, the venous pressure is higher and the prognosis more serious than if the obstruction is above the entrance of the azygos vein. However, the external evidences of collateral circulation are less marked from the lesions occurring below the entrance of the azygos vein. One patient with aortic aneurysm lived nineteen years after the diagnosis of obstruction was made.[29] The nature of the primary disease is obviously the factor of most importance in the prognosis. Patients tolerate obstruction of the superior vena cava itself surprisingly well and often for long periods of time.

The youngest patient with obstruction of the superior vena cava whose case has been reported was a 2-month-old baby suffering from spontaneous pneumothorax.[49] The oldest patient was a 93-year-old man who had thrombosis of the superior vena cava with extensive collateral circulation.[36]

A total of 434 cases of obstruction of the superior vena cava have been reported up to January, 1947. This number probably does not really reflect the rarity of the syndrome, however, as it is such a dramatic entity that observed cases are likely to have found their way into the literature.

In a review of 85,000 consecutive admissions to the White Memorial Hospital in Los Angeles, Calif., only four examples of this syndrome could be found. This suggests an incidence of approximately one case among 21,250 general hospital admissions. Two of these cases are reported in this paper.

CASE REPORTS

CASE 1.—This patient was a 62-year-old Mexican man who entered the White Memorial Hospital Sept. 20, 1946. For two weeks prior to his admission he had noticed cough, progressive

dyspnea, orthopnea, and edema of the face and upper extremities. For one week prominent anterior thoracic veins had been noted. He had had no edema of the lower extremities or sacrum, no chest pain, and no hemoptysis.

Past history revealed that a chronic, nonproductive cough had been present for several months. A senile type of diabetes mellitus which had apparently been well controlled had been known for twelve years. No important family history could be elicited.

Physical Examination.—On physical examination the patient was seen to be a well-developed, rather obese, elderly Mexican. He was markedly orthopneic and showed extensive edema of the face and upper extremities. Moderate cyanosis of the lips and nail beds was present. The blood pressure was 155/80 bilaterally. The pulse was 96 per minute, the respiration was 32 per minute, and the temperature was normal. His face, especially the eyelids, was so edematous that the eyes were nearly closed. The pupils were equal and reacted to light and accommodation. The ophthalmoscopic examination was normal except for moderate venous engorgement. The

Fig. 1.—Case 1. A roentgenogram of the chest showing mediastinal widening and infiltration in the left base.

ears, nose, and throat were not unusual. The neck was edematous, and markedly engorged veins could be seen. The thyroid gland was not palpable. There were large, dilated, tortuous veins over the entire anterior chest wall. Patches of dilated venules were scattered over the anterior chest and axillae. Impaired resonance to percussion was noted over the left posterior base, with decreased breath sounds and tactile fremitus over this same area. Numerous fine, moist, inspiratory râles were present in the right base, while the apices were clear to auscultation. The heart was not significantly enlarged. A Grade 2, blowing, apical, systolic murmur was present. The aortic second sound was loud and snapping. No thrills were felt. The abdomen was obese but no organs, masses, tenderness, or ascites were found. The genitalia were normal. The right leg had been previously amputated above the knee. There was no edema of the left ankle, but marked pitting edema was present in the upper extremities. The neurological examination was negative.

Laboratory findings were as follows: The urinalysis was normal except for 0.25 per cent sugar being present. The red blood cell count was 4.06 million, the hemoglobin was 13 grams per 100 c.c., and the white blood cell count was 16,850, with 80 per cent polymorphonuclear neutrophiles. The orthodiagram showed marked widening of the mediastinum, especially to the right, with fluid being present in the left lung base (Fig. 1). No unusual aortic pulsations were noted. The electrocardiogram was normal except for lowered R waves in the chest leads.

The tentative diagnosis was obstruction of the superior vena cava probably due to mediastinal lymphoblastoma. Deep roentgen therapy was given to the mediastinal area. Some improvement of the dyspnea and edema was noted and the patient was discharged on Oct. 4, 1946. He was readmitted to the hospital on Oct. 25, 1946, in a moribund state. His dyspnea was marked and his eyelids were swollen shut, yet no edema of the lower extremities was present. He died a few hours later.

Necropsy.—The upper anterior mediastinum was found to be occupied by a large, infiltrating tumor mass. The wall of the superior vena cava had been invaded by tumor tissue and its lumen was occluded by a thrombus which extended into both innominate veins. The microscopic diagnosis of the tumor was Hodgkin's sarcoma.

Fig. 2.—Case 2. Photograph of anterior chest wall showing dilated veins. Note the patch of dilated venules to the left of the upper sternum and over the left costal margin.

Comment.—This case is an example of the commonest form of thrombosis of the superior vena cava. As was the case in this instance, the thrombus is usually secondary to invasion of the vein wall by a malignant mediastinal neoplasm.

CASE 2.—The patient was a 45-year-old white man who entered the White Memorial Hospital on Nov. 4, 1946. He complained of "flushing and swelling" of the face, head, and neck, which had been present for two years. He had also noted dilated anterior chest veins for one and one-half years. Probably these symptoms had developed gradually, as the patient could give no exact date as to their onset. The sensation of flushing and fullness of the face and head was aggravated consistently by lying down or by stooping and by exercise. Edema of the eyelids and hands had been noted by the patient on arising in the morning. Tightness in the throat and slight dyspnea were noted upon exertion. No orthopnea, cough, wheezing, hoarseness, weight loss, or chest pain was ever experienced. Edema in the lower extremities was never noted. Fever had not been present at any time and enlarged lymph nodes were never found.

Fig. 3.—Case 2. Infrared photograph showing widespread dilatation of the veins of the anterior chest.

Past history did not reveal chest trauma, pulmonary tuberculosis, syphilis, or any other pulmonary, cardiac, or systemic illnesses. The patient had had gonorrheal urethritis twenty-four years previously.

Physical examination showed a well-developed, well-nourished white man in no acute distress, but anterior chest veins were markedly dilated and the face showed a dusky, flushed appearance. The blood pressure was 130/80 in both arms, the pulse was 84 per minute, the respiratory rate was 20 per minute, and the temperature was 98.6° Fahrenheit. The skin was clear except for a deep flushing of the face. The face and lips were slightly cyanotic. The ears, nose, throat, and eyes were not unusual and no evidence of Horner's syndrome was found. No particular engorgment of the neck veins was apparent, the thyroid gland was not palpable, and there was no cervical adenopathy. Large, tortuous veins covered most of the anterior chest wall. The largest of these veins extended downward over the abdomen and nearly to the pelvic brim (Figs. 2 and 3). These vessels filled from above at all levels. The heart was not enlarged. No murmurs were heard. Sinus rhythm was present. The lungs were clear throughout. A firm node, 1.0 cm. by 1.0 cm., was felt in the left axilla. The examination of the abdomen was normal except for the presence of large veins continuous with those on the anterior chest. No edema or deformities could be found in the lower extremities. The genitalia and the neurological examination were normal.

Laboratory Findings.—Laboratory findings revealed the following: Two urinalyses were normal and the Wassermann reaction was twice reported to be negative. The red blood count was 5.1 million and the hemoglobin was 16 grams per 100 c.c. of blood. The white blood count was 8,500 with a normal differential picture. The orthodiagram of the heart was not unusual. No mediastinal widening or abnormal pulsations were found. A sternal marrow study was reported as normal. A biopsy of the slightly enlarged left axillary lymph node revealed normal lymphoid tissue.

Fig. 4.—Case 2. Venograms showing dilated collateral veins of the anterior chest and evidence of venous obstruction in the region of both innominate veins. Left anterior oblique view of the right side.

Special Examinations.—In the right arm the venous pressure was 270 mm. of saline and the arm-to-tongue circulation time with magnesium sulfate was 25 seconds. In the left arm the venous pressure was 360 mm. of saline and the arm-to-tongue circulation time was 29 seconds. Normal venous pressure readings were found in the lower extremities. Venograms were made by the injection of 40 c.c. of 70 per cent Diodrast solution into the two respective antecubital veins as rapidly as possible through 16-gauge needles while serial roentgenograms were being taken. These venograms demonstrated almost complete obstruction of the superior vena cava and of the innominate veins as well (Fig. 4).

The patient has remained as he has been described for six months under observation. He carries on his work as a telegraph operator without difficulty and does not appear to be getting worse. In fact, many of his complaints are better. This improvement is probably due to improved collateral circulation.

Comment.—The history, the physical findings, the elevated venous pressures, and the definite evidence presented by the venograms are ample proof of the diagnosis of obstruction of the superior vena cava. To state the cause of the obstructing process with finality is difficult. All the evidence strongly suggests that the obstructing lesion is intraluminal. It is very probable that the causative factor was thrombotic in nature, and in view of the lack of evidence of any extraluminal lesion, one may suggest that a "primary" thrombosis of the superior vena cava is present. Several somewhat similar cases have been reported which ascribe the thrombus formation to "mediastinal fibrosis." However, in the majority of these cases some evidence of contributory mediastinal disease, such as syphilis or tuberculosis, was presented. No factors were found in this case which ordinarily are considered to promote thrombosis of the superior vena cava. Consequently, it is felt that this case may represent one of the rare primary cases of thrombosis of the superior vena cava.

SUMMARY AND CONCLUSIONS

1. The literature on obstruction of the superior vena cava has been reviewed and the 125 cases reported since 1934 have been collected and analyzed briefly.

2. Two additional cases, one of unusual interest, are reported in detail.

3. An outline of the important points in the diagnosis of the syndrome due to obstruction of the superior vena cava is presented.

4. Treatment, prognosis, and incidence have been discussed briefly.

The author wishes to thank Dr. John E. Peterson and Dr. Varner Jay Johns, Jr., for their kind permission to use the two cases presented in this paper.

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CONGENITAL DEXTROCARDIA WITH SITUS INVERSUS COMPLICATED BY HYPERTENSIVE HEART DISEASE; REVERSAL OF HYPERTENSIVE CHANGES FOLLOWING THORACOLUMBAR SYMPATHECTOMY

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WHILE dextrocardia with or without situs inversus is not a rare condition, its incidence having been estimated by LeWald[1] to be one in 35,000 Army recruits and by Parson[2] to be two in approximately 15,000 private patients, the finding of dextrocardia in association with acquired organic heart disease is exceptionally rare. Manchester and White[3] reviewed reports on dextrocardia from the time of Aristotle and found that it is not rare. In the cases reported, the only ones similar to the case to be presented are those reported by Willius[4] in 1931 and the case reported by Manchester and White in 1938. However, as far as can be determined, this is the first case of dextrocardia complicated by hypertension and cardiovascular disease in which reversal of the electrocardiographic picture occurred as a result of a Smithwick thoracolumbar sympathectomy.

REPORT OF CASE

A. B., a 35-year-old chief petty officer in the United States Navy, was admitted to the hospital on May 6, 1946, because of headaches, dizziness, and hypertension. Aside from attacks of palpitation associated with very rapid pulse occurring sporadically over a period of ten years, he had been in excellent health and had performed the arduous duties of a chief petty officer in wartime. There had been no illness except for the usual childhood diseases. He had a tonsillectomy in 1942 and a broken right tarsal navicular bone in June, 1945. He smoked an occasional cigar, drank beer and coffee occasionally, and denied any venereal disease. He had been married five years and had no children. About three months prior to the time of hospital admission, the patient began to complain of frequent headaches, particularly on change from a supine to an upright position. The headaches had been associated with dizziness and a feeling of lightheadedness and lasted from a few hours to several days. Because of these complaints and the presence of hypertension, the patient was admitted to the hospital for evaluation.

The family history revealed that the father had died from hypertension and heart disease at the age of fifty-three; the mother was living and well; one brother had died as a result of drowning, and four sisters were living and well.

Physical Examination.—The patient was heavy set and gray haired, and appeared older than his stated age. His temperature was 98.6° Fahrenheit. His pulse was regular at the rate of 62 per minute and his respiratory rate was 18. Blood pressure was 180/130. He was 71 inches tall and weighed 210 pounds. The only significant finding in the examination of the head and neck

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The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department or the naval service at large.

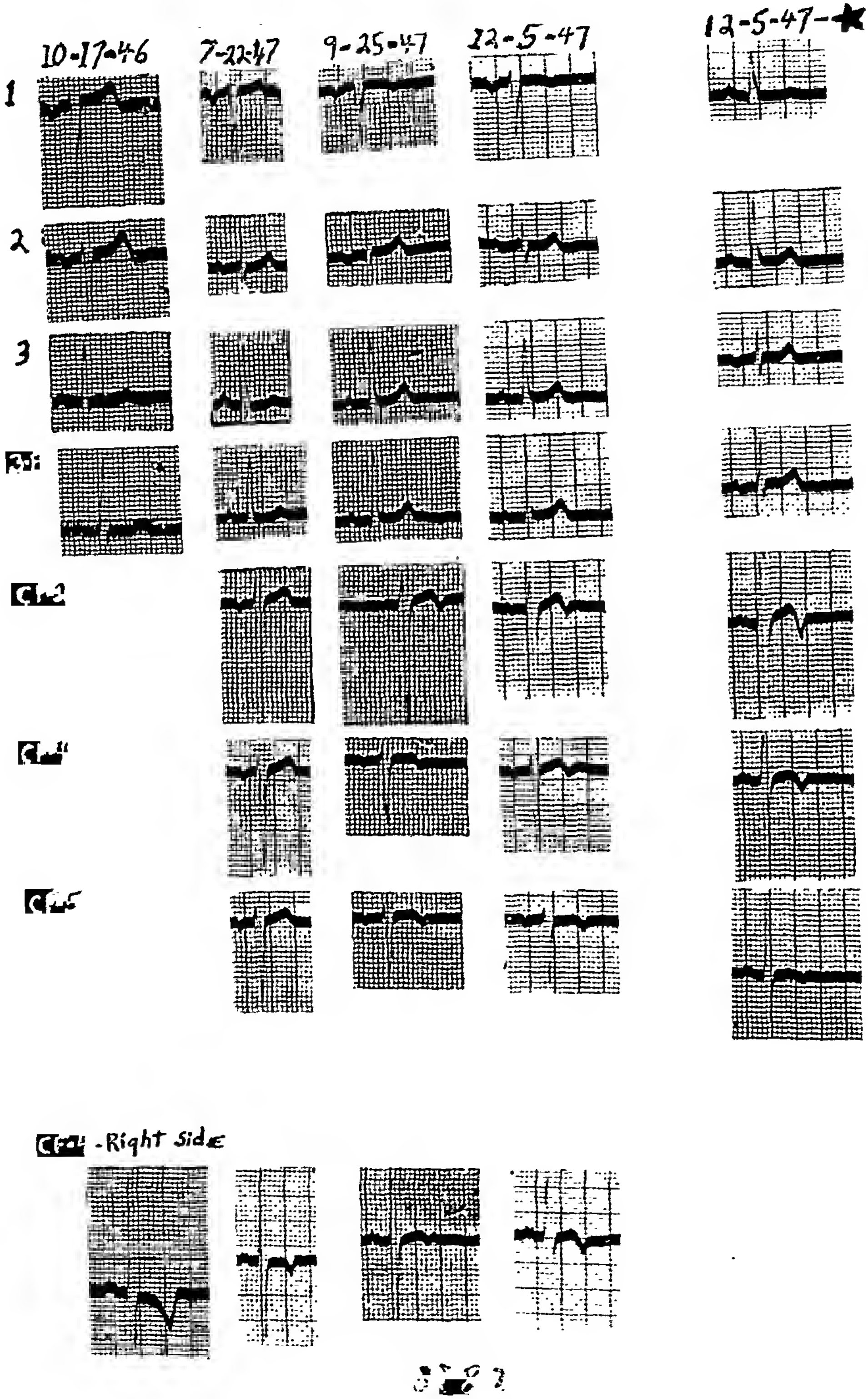


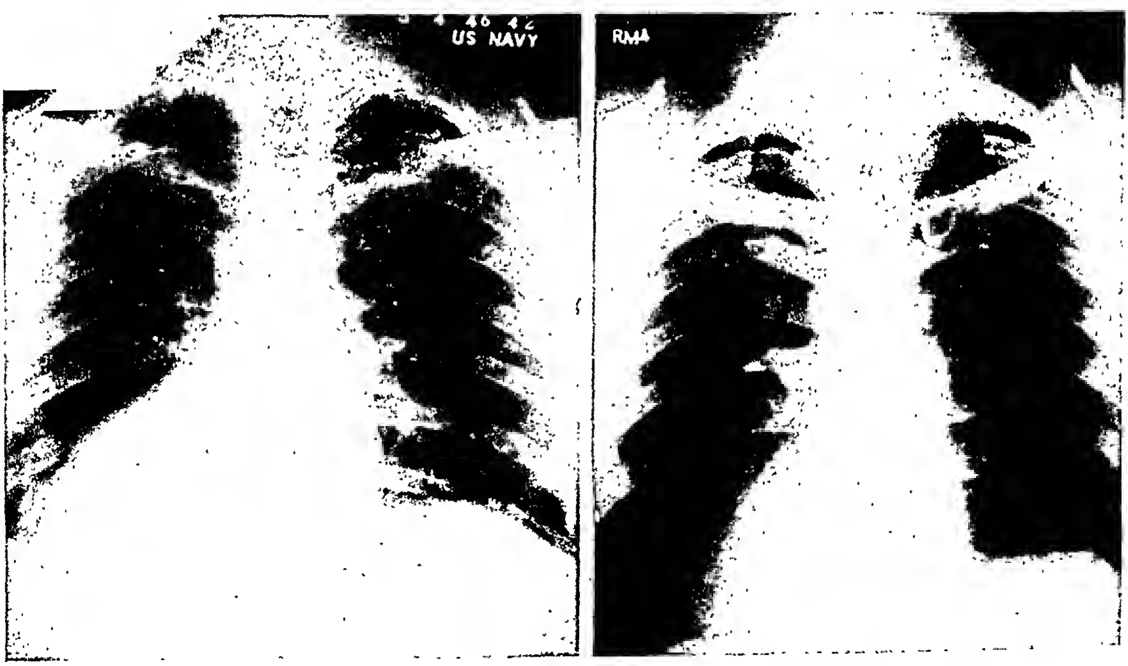
Fig. 1.—10/17/46: Original electrocardiogram showing the picture of dextrocardia complicated by "left" ventricular strain. 7/22/47: Twenty days after second stage sympathectomy: essentially no change. 9/25/47: Signs of "left" ventricular strain are disappearing. 12/5/47: Further improvement. 12/5/47*: Tracing taken with the limb leads reversed.

was that the ocular fundus adjacent to the disc showed slightly increased glial tissue with several instances of arteriovenous compression at the crossings. The ratio of the width of the arteries to the width of the veins was decreased with an irregularity in the caliber of the arteries and a widening of the light streak. The picture was that of early hypertensive retinopathy, Grade 1 to 2.

The apical impulse of the heart was palpable outside the midclavicular line 11.5 cm. to the right of the midsternal line in the right fifth intercostal space. The left border showed dullness 3.0 cm. to the left of the midsternal line in the fourth intercostal space. The second sound was louder in the left second intercostal space, which in this case corresponded to the second aortic sound, than in the right second intercostal space. There were no murmurs and no arrhythmias. The pulses were full, regular, and equal. There was no evidence of cardiac decompensation. The physical examination was otherwise negative.

Roentgenologic examination of the chest revealed transposition of the heart and slight cardiac enlargement to the right (Fig. 2, *A*). The aorta extended upward to the right and the aortic arch could be visualized in the right anterior oblique view. The left leaf of the diaphragm was higher than the right and diaphragmatic excursion was normal. Gastrointestinal examination demonstrated a transposition of the abdominal organs.

The electrocardiogram (Fig. 1) showed normal sinus rhythm, a ventricular rate of 60, marked right axis deviation, a P-R interval of 0.16 second duration, and a QRS complex of 0.08 second duration. The P waves and the QRS complexes in Leads I and II were inverted, while the T waves in all limb leads were upright. The T waves in Lead IV F, which was taken over the cardiac apex on the right side, were inverted.



A. *B.*

Fig. 2.—*A*, Teleroentgenogram taken 5/4/46. *B*, Teleroentgenogram taken 9/9/47.

Laboratory studies, including complete blood count, sedimentation rate, and Kahn, blood chemistry, urinalysis, and renal function tests, were all within normal limits. Blood pressure remained persistently elevated between 154/118 and 190/144.

The sodium amytal test lowered the blood pressure to 120/90 within three hours. A cold pressor test caused a rise in blood pressure from 156/120 to 198/180 within thirty seconds and a return to 166/140 within ten minutes.

At first the patient was placed on conservative management, including sedation and a reducing diet, in order to evaluate his symptoms. On Feb. 6, 1947, a left thoracolumbar sympathectomy from the eighth thoracic to the third lumbar ganglion was performed. The patient

withstood the procedure well, but his postoperative course was complicated by a pleural effusion and pneumothorax which required repeated aspirations. He was given time to recuperate sufficiently and on July 2, 1947, a right thoracolumbar sympathectomy from the fourth thoracic to the second lumbar ganglion was performed.

The patient recovered from this procedure rapidly except for an attack of auricular tachycardia which persisted for five days and was eventually controlled by quinidine. Blood pressure readings ranged from 108 to 120, systolic, and from 60 to 80, diastolic, for the first few weeks. The patient noted some hypotensive weakness and was provided with an abdominal belt. On Dec. 5, 1947, the patient was seen again and at this time he was completely asymptomatic, having been entirely free of any episode of palpitation and tachycardia for the first time in ten years. His blood pressure was 125/88. The eye grounds revealed a slight narrowing of the arteries with two instances of slight arteriovenous compression. The right border of cardiac dullness was 10.0 cm. to the right of the midsternal line and the remainder of the physical findings were essentially unchanged.

Postoperative electrocardiographic examination showed a normal sinus rhythm. The P-R interval was 0.17 second, while the duration of the QRS complex was 0.10 second. The P waves and the QRS complexes in Lead I were inverted, and there was marked right axis deviation. However, the T waves in Lead I, previously upright, had now become inverted.

DISCUSSION

Despite the fact that he had been examined physically on numerous occasions during the previous ten years because of episodes of palpitation and tachycardia, this patient had never been discovered to have dextrocardia until admission to the hospital, where this was confirmed by electrocardiographic and x-ray studies. The interesting feature of the electrocardiogram was that the T wave in Lead I was upright and the T wave in Lead IV F, taken over the cardiac apex on the right side, was inverted, indicating that this was the picture of "left" ventricular strain superimposed upon that of dextrocardia. In view of the fact that this was rapidly progressing, having appeared since the patient's last annual physical examination and because it was associated with symptoms and early eye-ground and electrocardiographic changes, the patient was placed upon a regime of sedation and weight reduction in an attempt to improve his condition.

However, after a period of nine months and a twenty-pound weight loss, there was essentially little change in his condition and, therefore, a left thoracolumbar sympathectomy was performed. Five months later a right thoracolumbar sympathectomy was performed, which, because of the patient's history of frequent episodes of tachycardia, was carried up to the fourth thoracic ganglion.

The patient's blood pressure returned to normal and has remained within normal limits. His symptoms completely disappeared and have not returned. The heart size has become smaller, as shown in Fig. 2, *B*, and the presence of "left" heart strain in the electrocardiogram has largely disappeared. As will be seen in Fig. 1, the evidence of heart strain was still present on July 23, 1947, approximately three weeks after the second operation, but on Sept. 25, 1947, was beginning to disappear. Confirmatory evidence of the disappearance of electrocardiographic signs of heart strain is shown in the tracing of Fig. 1* which was taken with the arm wires reversed, thus correcting for the dextrocardia.

SUMMARY

A case of congenital dextrocardia with situs inversus complicated by cardiovascular disease is presented. The interesting features are that the symptomatic, roentgenographic, and electrocardiographic findings due to hypertension were reversed by a Smithwick thoracolumbar sympathectomy, leaving the patient with his original congenital anomaly. There is no record of any other similar case, but presumably, if sympathectomies in hypertensive disease become more frequent, other such cases will be encountered.

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CONGENITAL ANEURYSM OF THE RIGHT ANTERIOR SINUS OF VALSALVA (INTERVENTRICULAR ANEURYSM) WITH SPONTANEOUS RUPTURE INTO THE LEFT VENTRICLE

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SPONTANEOUS rupture into the left ventricle of a congenital aneurysm of the right anterior sinus of Valsalva of the aortic valve is an occurrence heretofore undescribed in the literature. Such a case is herewith presented along with a brief discussion of the condition and of the interesting clinical aspects involved.

CASE REPORT

A. S., a 38-year-old Negro mechanic, was first admitted to Gallinger Hospital on Dec. 2, 1946, with the complaints of swollen feet of three days' duration and cough of two months' duration. He had apparently been perfectly well until the development of a "hacking cough," which was productive of a white, foamy sputum two months prior to admission. This persisted, and one and one-half months before admission, he began experiencing mild dyspnea on exertion which soon became severe and progressed to orthopnea. One month before admission, while working, he experienced a sudden dull midsubsternal pain which radiated to both the right and left upper abdominal quadrants. This pain persisted for several hours and was aggravated by numerous coughing spells. Two and one-half weeks later he began experiencing nausea and vomiting following his coughing spells. A progressive swelling of his feet occurred during the three days prior to his admission.

At the age of 24 years a vague attack of "rheumatism" had occurred. He had had an untreated "penile sore" lasting for two weeks at the age of 28 years. No serologic test for syphilis was performed at that time. During the two years prior to his hospitalization he had been hoarse as a result of undetermined reasons.

Physical examination on admission revealed a chronically ill and orthopneic Negro man, who appeared to be his stated age. The blood pressure was 180/40 to 20; the pulse was 100 per minute and of the waterhammer type; respirations were 24 per minute; and the temperature was 98.6° Fahrenheit. The anterior cervical and inguinal lymph nodes were palpable and small. The neck veins were slightly engorged and pulsating. The respirations were rapid and shallow. Crepitant râles were heard over both lungs. The heart was enlarged. Its left outermost border was 14 cm. from the midsternal line in the sixth anterior intercostal space. The point of maximal impulse was in the fifth left intercostal space at the anterior axillary line. A blowing aortic diastolic murmur was transmitted along the left sternal border to the apex and to the left axilla. A localized, soft, aortic systolic murmur was also described, as were a harsh apical diastolic murmur and a long, soft, apical systolic murmur. The rhythm was regular. The abdomen was moderately distended with bulging in the flanks. There was a questionable fluid wave and a palpable, tender liver which extended downward to the level of the umbilicus. There was 1 to 2 plus pitting edema of the legs, ankles, feet, and sacrum. The remainder of the physical examination, including the neurological, was essentially negative.

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Laboratory examinations revealed a negative blood Kahn test on two occasions and a urea nitrogen of 10 mg. per cent. An electrocardiogram showed left axis deviation, right bundle branch block, and a questionable, associated first degree A-V block. An x-ray film of the chest disclosed moderate pulmonary congestion and enlargement of the heart downward and to the left with a normally outlined aorta. The transverse diameter of the heart was 19 cm., while that of the chest was 32 centimeters.

The patient's congestive heart failure was controlled by the tenth hospital day after he had received digitalis, Mercupurin, and ammonium chloride therapy. Because of a persistent hoarseness a laryngoscopic examination was performed on the fifteenth day and chronic laryngitis was diagnosed. Nineteen days after admission he was released against the advice of the staff.

On Jan. 10, 1947, he again returned to the hospital with complaints similar to those on the previous admission. Physical examination at that time revealed a blood pressure of 160/40 and edema of the legs, ankles, and feet of greater severity than previously. Abdominal shifting dullness without a fluid wave was present. The remainder of the physical examination was essentially the same as that of the previous admission. Treatment consisted of digitalization and diuresis with Mercupurin and Aminophyllin. A venous pressure of 310 mm. H_2O was obtained on admission. An x-ray film of the chest disclosed a picture similar to that on the first admission. A repeat blood Kahn test was negative and the blood urea nitrogen was 13 mg. per cent. He was discharged on Feb. 7, 1947, to be followed in the cardiac clinic.

The final admission was one month later on March 7 when he again presented a history similar to that of the two preceding admissions. For a week prior to that admission he had failed to take diuretics and digitalis as prescribed. The blood pressure was 165/50, the pulse was 96 per minute, the respirations were 24 per minute and the temperature was 99° Fahrenheit. The lungs revealed fine inspiratory râles at the left base and an absence of breath sounds at the right base. The heart was enlarged as described on previous admissions. A loud mid-diastolic murmur with its maximum intensity in the fourth left intercostal space at the sternal border was transmitted downward to the apex. A systolic apical murmur which was transmitted to the left axilla and angle of the left scapula was also described. The remainder of the physical examination was essentially unchanged from the previous admissions. A venous pressure of 350 mm. H_2O rising to 450 mm. on right upper quadrant pressure was obtained on admission. A blood Kahn test was negative.

Several mild bouts of hemoptysis occurred four days after admission. An x-ray film of the chest at that time showed congestion with fluid at the right base and a density over the left costophrenic angle which was interpreted as a possible pulmonary infarct. A phlebothrombosis or thrombophlebitis of the upper or lower extremities was considered unlikely at that time. However, on the following day, because of bilateral calf tenderness and another bout of hemoptysis, a bilateral femoral vein ligation was performed. During the next two days several more bouts of hemoptysis occurred and the râles persisted at the left base. On March 16 he developed a moderately severe substernal and epigastric pain which was accompanied by a systolic blood pressure of 120, a pulse of 110 per minute, and roughened breath sounds and wheezes over both lung bases. Moderate upper abdominal tenderness was elicited.

He expired on March 17 after having experienced a rapid downhill course following his bout of substernal and epigastric pain.

Clinical Diagnosis.—(1) syphilitic aortitis with aortic regurgitation; (2) possible rheumatic heart disease; (3) congestive heart failure; and (4) pulmonary infarction.

Necropsy Report.—The pericardium revealed no abnormality; there were no pericardial adhesions, and 80 c.c. of clear, straw-colored fluid was present in the pericardial sac. The heart weighed 775 grams. It was greatly enlarged, firm in consistency, and was covered with a moderate amount of epicardial fat. On section, all chambers of the heart were found to be greatly dilated and there were no thrombi or emboli present. The tricuspid valve measured 16 cm. in circumference. Its cusps were moderately edematous at the tips and contained thin atherosclerotic plaques at the bases. The right ventricular wall measured 7.0 mm. in thickness and the papillary muscles were markedly hypertrophied. The chordae tendinae were not unusual and the pectinate

muscles were flattened. The pulmonary valve was dilated and measured 8.2 cm. in circumference. Several transverse fenestrations which were 5.0 mm. in length were present at the free edge of each cusp. The mitral valve was greatly dilated. It measured 15 cm. in circumference and its cusps were moderately thickened along the line of closure. The left ventricular wall measured 16 mm. in thickness and the papillary muscles were markedly hypertrophied. The chordae tendinae were slightly shortened, fused, and thickened; the pectinate muscles were flattened. The aortic valve measured 7.5 cm. in circumference at the ring. A transverse fenestration which was 3.0 mm. in length was present on the posterior cusp. It extended from the border of the left commissure onto the cusp and was parallel to and 1.0 mm. from the free edge of the cusp. The

Fig. 1.—Open left ventricle and aortic valve showing the large, gaping perforation of the right anterior sinus of Valsalva aneurysm.

right anterior cusp was slightly thickened along its free edge and was the seat of an aneurysm of the sinus of Valsalva. The aneurysm was a downward extension of the right anterior sinus of Valsalva into and dissecting the membranous portion of the interventricular septum. This aneurysm or sinus extended downward for a distance of 4.0 cm. below the level of the most inferior portion of the posterior and left anterior cusps to the trabeculated portion of the interventricular septum and measured 6.0 cm. in width. It produced its greatest bulge into the cavity of the left ventricle and lesser bulges into the cavities of the right auricle and right ventricle. A gaping perforation which measured 4.0 cm. in length was present on the left ventricular aspect

of the aneurysmal bulge and was located with its upper end at a point 6.0 cm. below the corpus arantii of the right anterior cusp, with its lower end 2.5 cm. inferior and to the right of the cusp. The inferior edge of this perforation was jagged, rough, and thickened and the superior edge was smooth. Figs. 1 and 2 show the opened left ventricle and aortic valve with the large, gaping perforation of the aneurysm of the right anterior sinus of Valsalva. The left anterior cusp was not unusual. The commissures of the cusp were not widened. The cusps were not rolled or shortened and their edges were free of abnormalities. The coronary ostia were patent, as were the coronary vessels throughout. A few yellowish-white, atherosclerotic subintimal plaques were noted in the descending thoracic and abdominal aorta. There was no gross evidence of syphilitic aortitis.

Fig. 2.—Opened left ventricle and aortic valve showing the large, gaping perforation of the right anterior sinus of Valsalva aneurysm.

Examination of the lungs revealed dense parietovisceral pleural adhesions in the right apex, left apex, left upper lobe laterally and posteriorly, and left lower lobe anteriorly, posteriorly, and laterally. These were associated with bilateral clear, straw-colored pleural effusions. The right pleural space contained 1,500 c.c. of fluid and there was 150 c.c. in the left pleural space.

The right lung weighed 1,100 grams and the left weighed 1,200 grams. Both showed marked congestion and edema. In addition, there was a thrombus in the medium-sized pulmonary artery which supplied the lower one-fifth of the left upper lobe. Distal to and surrounding this thrombosed vessel was a deeply hemorrhagic, firm triangular area. The thrombosed vessel represented its apex and the lung periphery, its base. The base of this triangular area measured 9.0 cm. in diameter and was on the anterolateral and inferior surfaces of the lobe. It extended 6.0 cm. distal to the apex. The bronchi were moderately congested and were filled with abundant frothy, blood-tinged fluid.

The liver was markedly enlarged and presented a "nutmeg" appearance; the spleen was somewhat atrophic.

The femoral veins were explored both proximal and distal to their ligated points. No abnormality was noted in the left; however, a thrombus was present in the right femoral vein proximal to the ligature. The proximal portion of the thrombus was attacked to the intima at the point of the ligature and its distal end was free in the lumen of the vessel.

The remainder of the gross examination revealed no abnormality.

Anatomical Diagnosis.—(1) Congenital aneurysm of the right anterior sinus of Valsalva of the aorta, extending within the vestibular portion of the interventricular septum, with perforation of the left ventricular wall of the aneurysm; (2) aortic valve insufficiency; (3) congenital fenestrations of the pulmonic and aortic cusps; (4) hemorrhagic infarct of the left upper lobe with thrombosis of a pulmonary artery; (5) pulmonary hyperemia and edema, severe; (6) cor bovinum; (7) hydrothorax, bilateral; (8) thrombosis of the right femoral vein; and (9) pleural adhesions, bilateral.

Microscopic Examination.—The gross and microscopic findings agreed essentially. Sections of the myocardium revealed a moderate degree of replacement fibrosis and marked muscle hypertrophy. The mitral valve was moderately thickened by hyaline and fibrous connective tissue. There was no evidence of rheumatic valvulitis. The anterior mitral papillary muscle contained a small amount of interstitial fibrous connective tissue. Numerous sections through the walls of the aneurysm revealed dense hyaline and fibrous connective tissue. The borders of the perforation were lined by endocardium and were composed of a dense fibrous and hyaline connective tissue stroma. However, this tissue was interspersed with rare small and large round cells and polymorphonuclear leucocytes. Vascular elements were scarce. A thin layer of endocardium lined all sections of the aneurysm.

The ascending and transverse aorta showed no microscopic evidence of syphilis or arteriosclerosis. There was no evidence of ulcerative endocarditis or mycotic infection.

A minimal amount of coronary atherosclerosis without appreciable narrowing of the coronary lumina was noted.

DISCUSSION

Aneurysms or aneurysmal dilatations may originate in one or more of the sinuses of Valsalva of the aortic valve.[1] These aneurysms are inferior extensions or excavations of the sinuses and their walls depend on the sinus or sinuses involved.

Of most frequent occurrence is an aneurysm of the right anterior sinus,[2,3] which is also called an interventricular aneurysm and which extends downward as it dissects the membranous, nontrabeculated aortic vestibule and interventricular septum. It does not involve the muscular or trabeculated portion of the interventricular septum. The cavity so produced is related to the left ventricle on one side and to the right auricle and right ventricle on the other. It produces bulgings of the corresponding walls of those chambers.

Even rarer are aneurysms of the left anterior and the posterior sinuses of Valsalva. The left anterior sinus is the only one related to the external surface

of the heart and, when dilated, produces a bulging into the pericardial sac to the left of the pulmonary artery. This also extends into the membranous, nontrabeculated aortic vestibular wall down to the muscular or trabeculated ventricular wall and internally is related to the cavity of the left ventricle. An aneurysm of the posterior sinus (noncoronary sinus) of Valsalva also extends downward in the wall of the aortic vestibule and bulges anteriorly into the left ventricle and posteriorly into the right and left auricles.

These aneurysms of the sinuses of Valsalva have been ascribed to syphilis, arteriosclerosis, mycotic infections, ulcerative endocarditis, and congenital lesions.[3,4,5]

Depending on the anatomic location of the aneurysmal bulge, a number of complications may ensue. These aneurysms frequently rupture although death may or may not occur immediately. The perforation may occur in the right atrium, right ventricle, left atrium, left ventricle, pericardial sac, mediastinum, pulmonary artery, superior vena cava, and left pleural cavity.[3,4,6,7] A rare case in which the pericardial sac was obliterated and the aneurysm eroded through the chest wall to rupture externally has been recorded.[4] The most frequent clinical picture of aneurysm of one or more of Valsalva's sinuses is that of aortic insufficiency or regurgitation,[3,8] due to dilatation of the aortic ring. Bulging of the aneurysm into the right ventricle may produce a clinical picture of stenosis or insufficiency of the tricuspid valve and/or pulmonary stenosis.[1] Encroachment of an aneurysm of the right anterior sinus on the A-V node or bundle of His in the interventricular septum often leads to heart block or other A-V conduction defects.[1,4,5,6] Rare cases of myocardial infarction caused by the compression of a coronary artery by an extrinsic aneurysm of the sinus of Valsalva have been reported.[4,9]

Death is usually the result of one or more of the mentioned complications and congestive heart failure.

The case reported here represents one of an aneurysm of the right anterior sinus of Valsalva of the aortic valve which bulged into the left ventricle and to a lesser degree into the right auricle and right ventricle and which ruptured into the left ventricular cavity. A congenital aneurysm with spontaneous rupture is postulated, as no pathologic evidence of syphilis, arteriosclerosis, mycosis, or ulcerative endocarditis was found. The spontaneous rupture of a similar congenital aneurysm into the cavity of the left ventricle has not to my knowledge been described heretofore in the literature. In retrospect, after having examined the rupture point of the aneurysm both grossly and microscopically and having reviewed the patient's clinical history, it seems probable that the perforation occurred some months before death, perhaps just prior to the patients' first hospitalization.

During his first two hospital admissions his congestive failure was fairly well regulated by digitalis and diuretics. However, on his final admission, control was unsuccessful, probably because of the associated femoral vein thrombosis and pulmonary infarction. His death was no doubt the result of congestive heart failure with superimposed pulmonary infarction.

Clinically, he presented a typical picture of aortic insufficiency; hence, the erroneous diagnosis of syphilitic aortitis was made. This is readily understandable because aortic insufficiency is the most frequent clinical finding in patients with aneurysms of one or more of the sinuses of Valsalva.[4] The murmurs heard in the region of the mitral valve were probably due to dilatation of the valve ring, as a result of congestive heart failure. No microscopic evidence of rheumatic valvulitis was found.

The electrocardiographic findings that were observed (bundle branch block and questionable A-V block) are frequently found in cases of aneurysms of the sinus of Valsalva involving the interventricular septum because of encroachment of the aneurysm on the A-V node or the bundle of His.[10]

SUMMARY

1. The clinical and post-mortem findings of a case of congenital aneurysm of the right anterior sinus of Valsalva with spontaneous rupture into the left ventricle are presented and discussed.

2. This is believed to be the first published report of such a case.

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ACUTE RHEUMATIC FEVER IN THE AGED

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THE acute rheumatic state is rare in the aged,[1,2,3,4] and rarer yet is an initial attack of acute rheumatic fever in the latter decades of life. It is the purpose of this communication to record a case in which an initial attack of acute rheumatic fever developed at 65 years of age. Rothschild, Kugel, and Gross[5] found only two cases of active rheumatic heart disease after the age of 50 and only one case after 60 years, but these were not initial attacks. In their study of 1,633 cases of rheumatic heart disease, DeGräff and Lingg[6] encountered only one patient who developed an initial infection past the age of 60. Rakov and Taylor[7] reported a case of rheumatic fever in a 61-year-old woman but stated in their summary that her initial rheumatic infection probably occurred in her childhood. Greene and Bennett[8] described a patient with an initial attack of rheumatic heart disease occurring at 64 years.

CASE REPORT

M. G., a white married woman, 65 years of age, had always been well and had done vigorous physical activity. She could not recall having had any symptoms of the rheumatic state, nor had any cardiac lesion ever been discovered. Except for a hysterectomy when she was 49 years old and four normal, full-term deliveries, she had required no medical attention. Questioning did not elicit any precipitating cause or the presence of any systemic disease prior to the onset of the present illness, which began three weeks before admission to the Beth-El Hospital on May 28, 1947. She had been well up to May 7, 1947, when she developed joint pains. The joint involvement was simultaneous, with the wrists, shoulders, knees, and ankles being particularly affected. There was pain, swelling, heat, and redness in the involved joints, and fever developed during the third week.

The patient presented the picture of an acute infection with hot, dry skin, anxious expression, and moderate prostration. The temperature was 103.4°F., the pulse rate was 98, and the blood pressure was 138/68. The wrists, shoulders, ankles, and knees were swollen, red, warm, and painful. There was limitation of motion of all joints. The skin was clear. The heart was not enlarged to percussion, and no murmurs or arrhythmias could be heard. The lungs were clear. The liver extended 2.0 cm. below the right costal margin but was not tender, and no pulsation could be felt. The spleen was not palpable. There was no edema of the lower extremities, except for the swelling of the ankles and knees. There were no other significant physical signs.

Laboratory examinations on the morning following admission revealed 11.0 Gm. of hemoglobin (71 per cent); a red blood cell count of 3,480,000; and a white blood count of 11,500. The differential count showed 78 per cent segmented neutrophiles, 15 per cent lymphocytes, and 7 per cent monocytes. The sedimentation rate was 18 mm. in seven minutes (Cutler method). Urinalysis was negative. An x-ray film of the chest on May 29 was read as follows: "The heart is of the

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aortic type and of normal proportional dimensions. The aorta, however, is elongated and widened, especially in the descending arcus. There is a calcific plaque in the arch. Hypertrophic osteoarthritic changes are noted in the dorsal spine." Roentgenologic studies of both hands showed hypertrophic osteoarthritis bilaterally. On May 31, the blood culture showed no organisms after forty-eight hours and an electrocardiogram revealed a P-R interval of 0.30 second.

Blood chemical examinations showed a serum protein of 6.6 Gm. per cent, with albumin of 3.7 Gm. per cent and globulin of 2.9 Gm. per cent. The blood urea nitrogen and sugar were within normal limits, and the uric acid was 1.5 mg. per cent. A Kline test was negative. Agglutination tests for brucellosis, typhoid, paratyphoid A and B, and typhus fever all were negative. Culture of a tonsillar swab revealed *Micrococcus catarrhalis* predominating with some pneumococci and staphylococci also present. The antifibrinolysin titer was 3 plus on June 10, and the same value was noted on June 18.

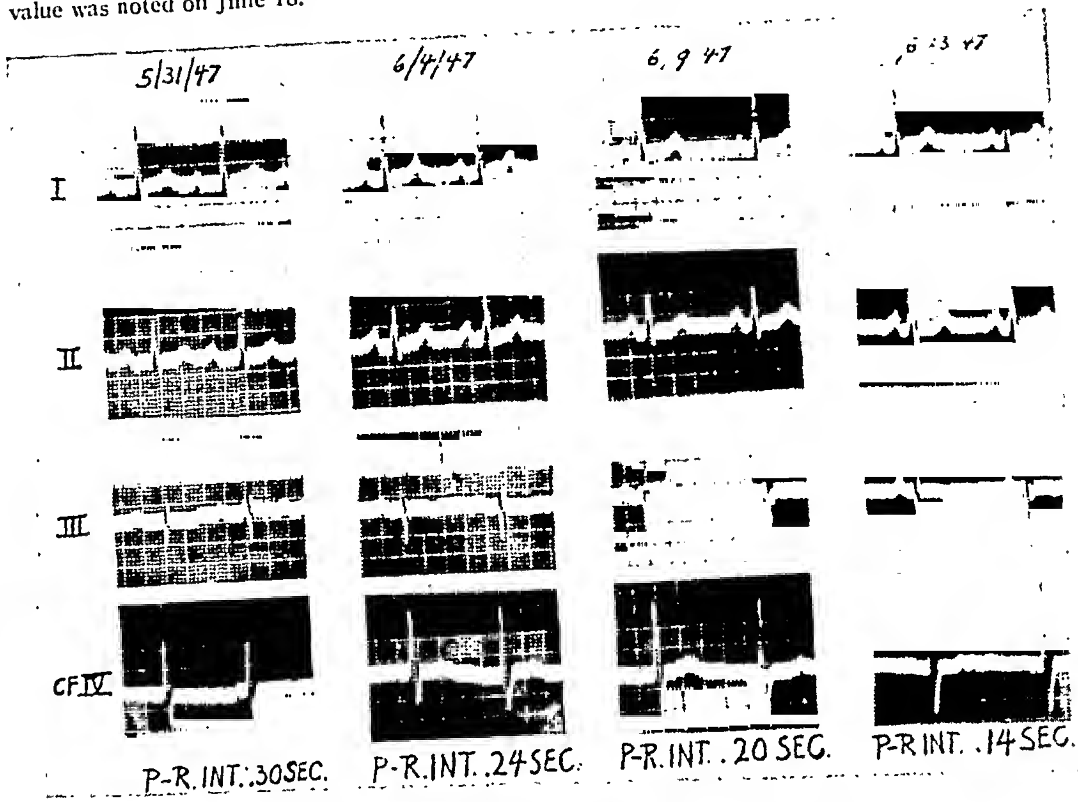

Fig. 1.—Serial electrocardiograms made during the acute illness.

Clinical Course.—The patient was confined to bed for six weeks. She received 20 grains of sodium salicylate and an equal amount of sodium bicarbonate four times daily from May 30 to June 29. From July 1 to the date of her discharge on July 16, she was given 15 grains of sodium salicylate three times daily, a 5.0 mg. tablet of vitamin K daily, a 250 mg. tablet of vitamin C each day, and two Feosol (three grains of ferrous sulfate) tablets three times daily. The fever, which had ranged between 100°F. and 103°F. for a week prior to admission, reached 102.6°F. on the first hospital day and gradually subsided to normal on the sixth day. Except for a temperature of 100.6°F. on the tenth day, she remained afebrile thereafter. The joint manifestations began to subside on the eighth day, with the swelling and warmth being alleviated first, while the pain on motion persisted until the second week. The joint symptoms completely subsided by the end of the third week. The pulse was 88 per minute on admission and ranged between 80 and 96 per minute during the first two weeks. Thereafter it fluctuated between 66 and 84 and never became irregular. No heart murmur was heard on admission. The con-

sulting cardiologist examined the patient on the eighth day and reported a faint systolic murmur at the apex. In the third week, a soft blowing diastolic murmur was heard along the left sternal margin in the fourth intercostal space, and persisted for four days. No murmur could be elicited thereafter.

An electrocardiogram taken on May 30 showed a P-R interval prolonged to 0.30 second. Subsequent electrocardiograms revealed the P-R interval to be 0.24 second on June 4, 0.20 second on June 10, and 0.14 second on June 23 (Fig. 1).

The sedimentation rate, which was 18 mm. in seven minutes (Cutler method) on the second day, was 18 mm. in twenty minutes on the eighth day, 18 mm. in forty minutes on the fifteenth day, and finally became 18 mm. in sixty-five minutes on the forty-second day. The leucocyte count was 11,500 on admission, declined to 7,750 on the eighth day, and remained from 5,000 to 6,000 after the third week. At the end of five weeks of treatment, the erythrocytes numbered 3,000,000 and the hemoglobin was estimated at 65 per cent. All urine examinations were negative. The blood salicylate level was 120 μg. per 100 c.c. on the seventh day, 380 μg. per 100 c.c. at the end of three weeks, and 168 μg. at the end of the fifth week.

At the time of discharge, there were no joint symptoms or complaints, and the temperature, P-R interval, sedimentation rate, and leucocyte count were all normal. There was, however, a persistent 3 plus antifibrinolysin titer.

COMMENT

It was apparent that the patient had suffered an initial attack of acute rheumatic fever despite her advanced age. Her previous history was negative for any previous attack of rheumatism, heart disease, or any joint pain; nor was there any antecedent history or positive evidence of the persistence of any specific infection.

Rheumatoid arthritis or chronic secondary infectious arthritis sometimes begins with the features of acute rheumatic fever. The initial and persistent involvement of small joints of the hands, feet, and spine and the comparative freedom from cardiac complications are suggestive features; and the persistence of periarticular swelling leading to obvious deformity confirms the diagnosis. However, none of these features was present in the case herewith reported.

Antitoxic or antibacterial serum therapy is often followed by serum sickness with polyarthritis as the chief symptom, but this patient had no coexistent urticaria and no history of serum treatment. She had received no penicillin treatment, which may occasionally cause a polyarthritis. There was no history of digitalis medication which might have caused the prolonged P-R interval. The persistently high elevation of the antifibrinolysin titer, although not specifically diagnostic, is a further link in the establishment of a diagnosis of acute rheumatic fever.

SUMMARY

A case is reported in which the initial attack of acute rheumatic fever occurred at 65 years of age. The presenting clinical picture included generalized joint involvement, fever, leucocytosis, a markedly prolonged P-R interval, and a rapid sedimentation rate. There was an excellent response to salicylate therapy. This response included an abatement of the joint symptoms, toxicity, and fever; and a return to a normal leucocyte count, sedimentation rate, and P-R interval. The absence of any previous heart disease or joint pains, the persistently elevated

antifibrinolysin titer, the secondary anemia, the transient abnormalities in the electrocardiograms, and the murmurs which appeared during the attack and then disappeared with recovery all contribute to the diagnosis of an initial attack of acute rheumatic fever despite the advanced age of the patient.

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Abstracts and Reviews

Selected Abstracts

Gomes, E. L., Capriglione, L., and de Souza, E. A.: Cardiac Changes in Uremia With Special Reference to Hyperpotassemia. Arq. de clin. 3:151 (Sept.), 1947.

The electrocardiographic changes commonly noted in preterminal stages of hyperpotassemia were demonstrated in three uremic patients. All subjects revealed a marked decrease in urinary volume and alterations in potassium level that were not necessarily correlated with the severity of the electrocardiographic changes. These changes were of the usual type with marked alteration of the P waves and of the QRS complexes and with increased amplitude of the T waves. First degree heart block, sinus arrest, and cardiac standstill occurred preterminally. The clinical signs of hyperpotassemia consisted of paresthesias, flaccid paralysis, and acute left ventricular failure. In two necropsied cases no particularly striking alterations of the heart muscle were noted.

HECHT.

Schlesinger, P., and de Moraes, J.: The Clinical Value of the Esophageal Electrocardiogram. Arq. de clin. 3:183 (Sept.), 1947.

The value of unipolar esophageal leads in conjunction with standard bipolar limb leads, unipolar limb leads, and precordial leads is demonstrated on twenty patients. The value of such leads in ventricular enlargement, in coronary insufficiency with and without myocardial infarction, and in auricular disorders is emphasized. The influence of position of the heart upon the auricular and ventricular pattern obtained has not been considered. A case of Chagas' disease with complete A-V heart block and an example of anomalous A-V conduction (Wolff-Parkinson-White syndrome) are included.

HECHT.

Winton, S. S.: Sinoauricular Block: An Analysis of Eleven Cases. Acta cardiol. 3:108 (Fasc. 3), 1948.

Eleven examples of the disorder are discussed. All patients revealed signs of organic heart disease and four had received digitalis at the time the block was present. In two instances the block disappeared spontaneously; in one, following the administration of atropine. Three of the patients demonstrated an uncomplicated sinoauricular block, while five were classified as sinoauricular block with Wenckebach phenomenon. An additional case of the latter type could be converted to 2:1 sinoauricular block by carotid sinus pressure. Nodal escape, nodal rhythm, and reciprocal conduction from ventricle to auricle to ventricle ("sandwiching") was noted in the remaining two patients.

HECHT.

Evans, W., Dick, P., and Evans, B.: Rapid Digitalization. Brit. Heart J. 10:103 (April), 1948.

Because there is no agreement on the best preparation and route of administration for inducing rapid digitalization, this study was designed to discover the most effective preparation for rapid digitalization, when given orally or intravenously, by comparing the effects on the same

patients of as many as possible of the following preparations: (1) strophanthin, (2) ouabain and K-strophanthosid, (3) Digoxin, (4) digitoxin, (5) lanatoside C, (6) digitalis leaf, and (7) tincture of digitalis.

Twenty patients with mitral stenosis or hypertension were selected. All had auricular fibrillation with a rapid ventricular rate and with slight to moderate congestive failure. All were on a normal hospital diet with fluids restricted. None had had digitalis for at least the preceding seven days. The order in which the drugs were given was deliberately varied from patient to patient. The consistency of the action of a drug in the same dosage and in the same patient was tested in only two individuals. In one instance, the effect was different and in the other, almost identical. In successive cases, however, the drugs produced the same result with remarkable consistency.

The fall in ventricular rate was regarded as the most satisfactory index of digitalization. A digitalis effect was classified as good when the fall in heart rate within four hours was 75 per cent of the maximal fall produced by any preparation in that patient, moderate when the fall in rate was between 50 and 75 per cent, and slight when below 50 per cent.

The authors found that strophanthin produced good effects only with a dose (1.0 mg.) which is larger than that generally regarded as safe. Strophosid (0.5 mg.) was superior to strophanthin yet did not produce the consistent results obtained from digitalis preparations and no justification was found for the continued use of either strophanthin or strophosid.

Digitalis nativelle, in a dose of 1.2 mg. orally, gave inconstant results and this dose was regarded as too small. No support was found for the contention that it is completely absorbed. Intravenously, a dose of 1.2 to 1.5 mg. gave consistently good results within two hours, which compared favorably with the results given by both Digoxin and lanatoside C, although the latter two frequently produced a more rapid effect in one hour.

The oral digitalization dose of Digoxin is regarded as at least 2.0 mg. and probably as much as 3.0 milligrams. Intravenously, the minimal full dose is regarded as 1.0 milligram. By this method, a good result was produced in most instances and a rapid effect in more than one-half. But it was inferior to lanatoside C in six of eight instances. Lanatoside C in a dose of 1.5 mg. produced a good effect in all instances.

When a digitalis effect is required within an hour, intravenous lanatoside C (1.5 mg.) or intravenous Digoxin (1.0 mg.) is recommended. When a digitalis effect is required within four hours, oral Digoxin (2.0 to 3.0 mg.) is recommended.

SOLOFF.

Dick, P.: The Relative Value of Digitaline Preparations in Heart Failure With Auricular Fibrillation. Brit. Heart J. 10:122 (April), 1948.

This study was undertaken to ascertain whether there was any variation in the value of six commercial preparations of digitaline available in Great Britain when dispensed to patients with heart failure or auricular fibrillation. Thirteen patients were selected; three of these failed to complete the study. Two had hypertension and eight had mitral stenosis. With one exception, all had received powdered digitalis leaf for prolonged periods. A test period of fourteen days was used. The apical rate was counted for three successive half minutes. The order in which the preparations were given was deliberately varied. In order to check the results, a second series of trials on seven other patients was carried out.

One preparation was much less effective than the other five in both series. This may have been due to differences in the procedure for manufacture of digitaline.

It is suggested that until a standardized procedure for the manufacture of digitaline is introduced, digitalis leaf should be used for continuous digitalization.

SOLOFF.

Glasser, A.: The Normal Electrocardiogram and Its Relation to the Body Build. Cardiologia 12:323 (Fasc. 6), 1947-1948.

Standard electrocardiograms of 193 healthy, robust, 23- to 58-year-old men were correlated with data of their body builds and a comparison has been made with similar series of tracings ob-

tained by other authors. A point is made of the fact that only leads taken simultaneously have been used for measurement. A P-R interval longer than 0.20 second was present in 3 per cent of the cases; there was no correlation of the duration of this interval with age. The mean angles α of the vectors were: of P, 45.5° (−13° to +80°); of R, 50.0° (−4° to +109°); of T, 38.7° (0° to +81°). The manifest value of R was larger in light than in heavy individuals. The ratio of vector T to vector R was greater in left than in right axis deviation.

The angle α of R was larger in tall, slender, and light men than in small, broadchested, heavy men. It decreased with age irrespective of blood pressure or type of body build. There was a definite inverse relation of this angle to the transverse horizontal square area of the thorax and a definite direct relation to the height of the thorax. An increase of 1.0 cm. in the latter was accompanied by an increase of 5° in the former. Age had no demonstrable influence on this angle. The left axis deviation type of the ventricular complexes displayed a smaller angle between the vectors R and T than the right axis deviation type.

BRUMLIK.

Polzer, K.: Rate and Rhythm in Acute Myocardial Infarction. Cardiologia **13**:1 (Fasc. ½), 1948.

Fifteen of fifty-one patients with acute myocardial infarction showed a temporary bradycardia during the first twenty-four hours caused by excessive sinus bradycardia, complete A-V block, or nodal rhythm. The author assumed that the response was of a reflex nature. However, most patients were under the vagal influence of large doses of morphine. The Q-T interval was usually prolonged over the predicted normal range.

HECHT.

Alvarez Mena, S.: The Normal Configuration of the Ensiform Lead (V_e). Rev. españ. de cardiol. **2**:1, 1948.

The configuration of 100 ensiform leads has been analyzed. When placed over the lower end of the xyphoid cartilage the electrode registers potential variations of the free wall of the right ventricle and of the adjacent interventricular septum. The pattern is similar to that obtained from other right ventricular regions.

HECHT.

Garcia, E., Arriba, O., and Lopez, F.: Diphtheria and Coronary Occlusion. Rev. españ. de cardiol. **2**:59 (July 31), 1948.

During the course of severe diphtheria in a 12-year-old boy a classical episode of myocardial infarction occurred on the fifth day of the disease. Characteristic electrocardiograms were obtained. As no other etiological factor could be implicated, the authors assume that an acute infectious arteritis of the coronary arteries had resulted in intravascular thrombosis. The patient died following this episode, but necropsy was not performed.

HECHT.

Calvino, J. M.: Obliterating Thrombosis of the Right Auricle. Report of Two Cases. Rev. cubana de cardiol. **1**:1 (Jan.), 1948.

The author presents the cases of two patients with heart disease whose clinical findings were characterized by dyspnea, paroxysmal in type, and typical signs of right heart failure. At necropsy, a pedunculated thrombus of the right auricle was found in each case. It was clear that some of the attacks of dyspnea, cyanosis, and right heart failure were due to obstruction of the tricuspid orifice by the freely movable thrombus.

The author reviews the literature and suggests that the diagnosis, if suspected during the life of the patient, may be confirmed by angiocardiography. Incomplete filling of the right auricle and narrowing of the valvular opening by the thrombotic mass may thus be demonstrated.

GOLD.

Malinow, M. R., Moia, B., Otero, E., and Garcia A.: Circulatory Changes Produced by Exercising Ischemic Muscle. I. Preliminary Observations. Rev. argent. de cardiol. 15:1 (Feb.), 1948.

Standardized weight-lifting exercises (lifting of five-pound weights forty times per minute over 5.0 cm. for three minutes) were performed on five normal subjects. A slight increase in heart rate and in mean arterial pressure was noted. The pressure changes reversed themselves regularly and a fall in systolic and diastolic pressures occurred on recovery. Exercising of an ischemic limb resulted in a slightly higher rise of arterial pressure with a lessened tendency to an overswing of pressure values below the resting value. The heart rate increased as before. Atropine and ergonovine did not greatly alter the response obtained. The studies are preliminary to similar observations in patients with intermittent claudication and to studies on the pathogenesis of pain arising from an ischemic extremity.

HECHT.

Del Zar, L. E., and Bronstein, J.: The Influence of Infiltration Anesthesia of the Precordial Region on the Occurrence of Precordial Pain and on Electrocardiographic Changes in Angina Pectoris. Rev. argent. de cardiol. 15:17 (Feb.), 1948.

Twenty or 40 mg. of 1 per cent procaine, given subcutaneously in the precordial area, prevented or attentuated the occurrence of precordial pain in seven of ten patients subjected to an exercise test. In eighteen patients the electrocardiographic changes on exertion were not altered by the procedure, even when pain was obliterated. A full explanation of the discrepancy is not given, but it appears unlikely that precordial procaine infiltration altered coronary blood flow, as has been suggested before.

HECHT.

Alzamora-Castro, V., Rubio, C. W., and Battilana, G. D.: The Systolic Murmur in Aortic Stenosis. Rev. argent. de cardiol. 15:25 (Feb.), 1948.

Simultaneous registration of arterial pulse curves and phonocardiograms reveal that the systolic murmur of aortic and pulmonic stenosis begins at the onset of the ejection period and fades toward the latter part of systole. The maximal intensity of the murmur coincides with the maximal ejection period.

HECHT.

Etala, F., and Berreta, J. A.: Anatomical-Clinical Study of a Case of Post-tachycardial Syndrome. Rev. argent. de cardiol. 15:133 (Feb.), 1948.

Cossio, González-Sabathié, Berconsky, and Vedoya, in three successive articles, have described a clinical picture which they called "post-tachycardial syndrome," based on the following data: (a) relatively young subjects, usually without demonstrable cardiac lesions; (b) repeated and prolonged attacks of paroxysmal tachycardia, mostly ventricular; (c) reversible cardiac enlargement; (d) electrocardiographic changes after the attack consisting of depression of the RS-T segment in one lead with elevation in another, inversion of the T wave, and prolongation of the Q-T interval; (e) gradual return of the electrocardiograph to normal within a few days; and, (f) at post mortem, the presence of a dilated and hypertrophied myocardium with absence of other lesions.

The authors report an additional case with post-mortem study. The histologic study failed to reveal any typical change in the myocardium or in the coronary system.

Even if the death in the reported case cannot be attributed with certainty to this syndrome, the latter cannot be considered as completely benign because it may be followed by sudden death or by heart failure.

LUISADA.

Stein, I. D., Harpuder, K., and Byer, J.: Effect of Sympathectomy on Blood Flow in the Human Limb. Am. J. Physiol. **152**:499 (March), 1948.

Plethysmographic studies in a small group of patients with various peripheral vascular diseases (thromboangiitis obliterans, arteriosclerosis, Raynaud's syndrome, cold injury, and essential hypertension) confirmed previous observations that sympathectomy fails to increase the resting blood flow within muscles, but does increase the skin circulation of the denervated extremity. The calf was used to test predominantly muscle blood flow, while the flow in the foot represented primarily skin circulation. Blood flow in muscles could be effectively increased by exercise, tissue heating, or release of temporary arterial occlusion. These procedures are known to release vasodilating metabolites. It is implied that sympathectomy will be useful clinically only for lesions or symptoms resulting primarily from deficient skin circulation.

HECHT.

Eckenhoff, J. F., Hafkenschiel, J. H., Foltz, E. L., and Driver, R. L.: Influence of Hypotension on Coronary Blood Flow, Cardiac Work, and Cardiac Efficiency. Am. J. Physiol. **152**:545 (March), 1948.

Hypotension was produced by the subdural injection of procaine hydrochloride or by the intravenous injection of tetraethyl ammonium chloride in anesthetized dogs whose coronary blood flow was being measured by the nitrous oxide method. Cardiac work and efficiency were calculated from venous catheterization data.

Diminished cardiac output with marked reduction in cardiac work accompanied the fall in blood pressure in seven of the eight experiments. Coronary blood flow declined in all instances (average, 25 per cent) but relatively less than cardiac work, which on the average fell 56 per cent. Cardiac efficiency, which is the work done divided by energy intake, declined 36 per cent. This would appear to indicate a decreased capacity of the heart to perform its work under these conditions, but evidence for such capacity is lacking, since the hypotension did not seem to be harmful to the experimental animal. The discrepancy is thought to lie in the concept of mechanical cardiac efficiency, the calculation of which fails to include the utilization of oxygen for factors other than actual mechanical work, such as the energy used for the maintenance of the cardiac muscle cells, or that required for isometric ventricular contraction. Cardiac efficiency, as calculated, is not a valid criterion of the heart's capacity for work under changing experimental conditions.

HECHT.

Galdston, M., and Steele, J. M.: Arterial Pressure Waves in a Patient With Coarctation of the Aorta. Am. J. Physiol. **152**:554 (March), 1948.

In addition to recording the usual arterial pressure pulse waves in an upper and lower extremity in a patient with coarctation of the aorta, the arterial tracing from a collateral artery connecting the arterial tree above and below the coarctation was recorded by the means of a Hamilton intra-arterial manometer. The pressure in the collateral vessel, the left subscapular artery, whose lumen measured 0.5 cm. in diameter, was 215/100. The pressure and the form of the pulse tracing were identical to those of the left radial artery although the collateral artery arose distal to the obstruction. The coarctation and the anatomical arrangement of the collateral circulation were confirmed by autopsy.

HECHT.

Lenel, R., Katz, L. N., and Rodbard, S.: Arterial Hypertension in the Chicken. Am. J. Physiol. **152**:557 (March), 1948.

Hypertension was consistently produced in chickens when saline solution was substituted for drinking water. After sixty days of saline intake the average systolic and diastolic pressures rose from the control average of 132/117 to an average of 182/154. Prompt fall in blood pressure followed withdrawal of the saline. The degree of hypertension was further increased by raising

of the salt concentration from 0.9 per cent to 1.2 per cent. Blood volume and hematocrit showed no significant changes.

Dehydration with loss of weight was the usual course of the chickens on the saline regime. No anasarca occurred except in one bird which died after forty-three days and showed pulmonary edema, pericarditis with effusion, and hyperemia of the other organs. After three months and two separate periods of salt ingestion, all of the chickens at autopsy showed hyperplasia and proliferation of glomerular tufts and Bowman's capsule with compression of the capillaries.

HECHT.

Campbell, W. N., Sokalchuk, A., and Penman, R.: Validity of T-1824 in Plasma Volume Determinations in the Human. Am. J. Physiol. 152:563 (March), 1948.

The estimation of plasma volume by T-1824 was reinvestigated in six subjects under basal conditions. Two injections of the dye were made at a thirty-minute interval, and blood samples drawn at ten, thirty (prior to second injection), and forty minutes. Calculations of the plasma volume on the ten-minute samples after each injection showed an average difference of but 1 per cent. This suggested that the dye method gave reliable results and that, if active removal of the dye during the early mixing period by the reticuloendothelial system occurs in man, it does not invalidate the determinations. That complete mixing of the dye had occurred at ten minutes was shown by the close agreement between the samples drawn simultaneously from each arm.

HECHT.

Sussman, A. H., Hemingway, A., and Visscher, M. B.: Importance of Pressure Factors in the Genesis of Pulmonary Edema Following Vagotomy. Am. J. Physiol. 152:585 (March), 1948.

The problem of the production of pulmonary edema in guinea pigs maintained on positive pressure artificial respiration was reinvestigated. Previously it had been reported that fatal lung edema occurred in vagotomized animals, but not in those with intact vagi. The authors found that neither group of guinea pigs developed pulmonary edema when the insufflation pressure was 6 mm. of mercury. At a pressure of 20 mm. Hg, however, massive edema occurred in all animals. Thus, no evidence was found to indicate that vagotomy has any effect on the pulmonary vascular system favoring edema.

HECHT.

Surtshin, A., Rodbard, S., and Katz, L. N.: Inhibition of Epinephrine Action in Severe Hypoxemia. Am. J. Physiol. 152:623 (March), 1948.

Severe hypoxemia was produced in anesthetized dogs by artificial respiration with 100 per cent nitrogen. The arterial pressure gradually increased for sixty to ninety seconds, but then fell rapidly. If the breathing of nitrogen was continued, death shortly ensued from circulatory failure, cardiac dilatation, and arrest in diastole.

When normal air breathing was instituted during the phase of hypoxemic pressure fall, the blood pressure promptly rose to levels above the hypoxemic pressure rise. This was attributed to the accumulation of pressor substances which fail to act in the absence of oxygen. When epinephrine was injected intravenously or intracardially during the hypoxemic depression, the usual pressor response was absent or markedly diminished until after air breathing was reinstituted, at which time the adrenalin effect was superimposed upon the usual posthypoxemic pressor effect. Thus, the effect of epinephrine seems to depend on oxygenation of the blood. It is implied that the clinical use of epinephrine in cases of marked hypoxemia is of no avail unless oxygenation of the blood has been accomplished.

HECHT.

Campbell, G. S., and Harvey, R. B.: Postural Changes in Vital Capacity With Differential Cuff Pressures at the Bases of the Extremities. Am. J. Physiol. 152:671 (March), 1948.

Vital capacity has been shown to decrease in changing from the standing to the recumbent position. The authors found a decrease of 185 c.c. in nine normal male subjects. When blood was

progressively pooled in all the extremities by cuffs inflated to the diastolic level, the decrease in the recumbent position was nullified. When the volume of blood in the extremities was kept constant by cuffs inflated to the systolic level, there was no change in vital capacity.

HECHT.

Froment, R., and Gallavardin, L.: Sinus Arrest With Intermittent Nodal Rhythm. Arch. d. mal. du coeur 41:113 (March), 1948.

Electrocardiograms of a 55-year-old man are presented which over a four-year period demonstrated a peculiar arrhythmia. Careful analysis of many records reveals the coexistence of a sinus rhythm (rate 70) and an A-V nodal rhythm. Frequently shorter and longer periods of intrinsic arrest of the impulse formation within the sinus node were observed which were regularly compensated for by the slower nodal rhythm. When the activity of the nodal center decreased, the sinus recommenced its activity. The sinus pauses could clearly be differentiated from ordinary sinoauricular block and were accentuated by vagal stimulation. The patient did not reveal any clinical symptoms or signs of heart disease.

HECHT.

Paterson, J. C., Slinger, S. J., and Gartley, K. M.: Experimental Coronary Sclerosis. I. Medial Degeneration as the Primary Lesion in Coronary Sclerosis of Cockerels. Arch. Path. 45:306 (March), 1948.

The authors report on the occurrence of a medial lesion which they consider to be of prime importance in the genesis of coronary sclerosis in chickens. They found that the incidence of coronary sclerosis in cockerels was the same whether or not dry cholesterol was added to their diet. The addition of cholesterol, however, accelerated the sclerotic process already established. They also found that a degenerative medial lesion preceded the intimal changes in treated and control cockerels.

The majority of control birds showed spontaneous arteriosclerosis, the most important change being in the media. The feature of this lesion was a hydropic degeneration with disruption of the elastica; a total lack of calcification sets this avian lesion aside from medial changes in other species. Round cell infiltration in the adjacent adventitia and some slight fibroblastic thickening in the overlying intima complete the picture of spontaneous coronary sclerosis as seen in these chickens.

Cholesterol feeding did not alter the incidence of this arterial degeneration, but added significantly to the intimal thickening, resulting in prominent foam cell aggregations, filled with lipoid material. These cells infiltrated the areas of medial hydropic degeneration and also the adventitial thickening, obscuring all other details by the formation of a nodular foam cell mass, sharply demarcated from the rest of the arterial circumference, and pouching inward into the lumen and outward beyond the normal adventitial confines. With massive foam cell infiltration, small points of calcification appeared.

The authors are unable to explain the pathogenesis of spontaneous arteriosclerosis in chickens. It involves the coronary arteries predominantly, and is often accompanied by a focal round cell infiltration of the myocardium, suggesting that infection may be the basis for the combined arterio-myocardial disease. The lesion is admittedly different from human atherosclerosis.

GOULEY.

Guenther, B., and Gareia Campo, M.: New Aspects of the Problem of Pressure Reactions. Rev. argent. de cardiol. 15:53 (March-April), 1948.

The authors suggest that evaluation of the reactivity to "cold pressor" tests be based on the ratio of rise in pressure to basal pressure. A pressure reaction of more than 20 per cent is considered excessive. This maximal limit is compared with the pressure volume curves of the aorta given by Bazett and a correlation between the two is found. By applying this concept, the authors find that hyperreaction is as frequent in normal subjects as in hypertensive patients.

LUISADA.

Post, R. S., Visscher, P. H., and Wiggers, C. J.: *Sequential Changes in Oxygen Consumption During Oligemic and Normovolemic Shock and Their Meaning.* Am. J. Physiol. 153:71 (April), 1948.

In standardized hemorrhagic shock in dogs, reduction in oxygen consumption is not a necessary concomitant of the irreversible state. Oxygen consumption, however, is drastically reduced immediately after the fall in arterial pressure. This remains low despite increased pulmonary exchange. Reinfusion of blood after irreversible circulatory changes have taken place resulted in a decided increase in the oxygen uptake over the normal values (average, 61 per cent). The early reduction in oxygen uptake following a large volume of blood loss is most likely secondary to the lowered cardiac output and lowered capacity to transport oxygen. The recovery of oxygen uptake during the latter part of the irreversible hypotensive period can be accounted for by the excess oxygen required for augmented respiratory activity. The large increase in oxygen consumption which follows a transfusion and continues even as circulatory failure redevelops is attributed to the combination of improvement in oxygen transport, continuance of augmented respiratory action, and oxidation of metabolic acids. The generally accepted hypothesis that irreversible circulatory changes are accompanied by reduced oxygen utilization is not conclusively supported by these and by other published observations.

HECHT.

Stacy, R. W., Whitehorn, W. V., and Hitchcock, F. A.: *Susceptibility of Cats and Dogs to Progressive Anoxia.* Am. J. Physiol. 153:87 (April), 1948.

In a comparative study of the responses of cats and dogs under barbiturate anesthesia to anoxic anoxia, it was found that dogs were able to withstand low oxygen saturation better than cats. The dogs hyperventilated to a much greater degree than the cats. Denervation of the chemoreceptors prevented hyperventilation, obliterated any species differences, and further reduced the anoxic tolerance of both cats and dogs. It would appear, therefore, that the cells of the medullary respiratory center are equally susceptible to anoxia. The increase in arterial pressure during anoxia is reversed in both species following chemoreceptor denervation. A theoretical expression of the relation between volume of ventilation and the inspired air is presented.

HECHT.

Hoff, H. E., and Nahum, L. H.: *Comparison of the Electrocardiographic Changes Produced by Heating and Cooling Epicardial and Endocardial Surfaces of the Dog Ventricle.* Am. J. Physiol. 153:176 (April), 1948.

Studies were carried out in eighteen dogs designed to determine the changes in direction of the T waves in the standard and precordial leads after warming and cooling of restricted areas of the endocardium and the overlying epicardium of both the right and left ventricles. Both endocardial and epicardial leads demonstrated an increase in the amplitude of the T waves when either the endocardial or the epicardial regions were heated. All leads showed inversion of T when either surface was cooled. The authors insist that their experiments lend no support to the theory that differences in rate of repolarization between epicardial and endocardial myocardium are responsible for the shape of the T wave, but they concede that T-wave inversion in precordial leads indicates repolarization delay in regions adjacent to the exploring electrode, while upright T waves signal delayed repolarization of distant regions.

HECHT.

Stoner, H. B., and Green, H. N.: *Bodily Reactions to Trauma. The Effect of Ischaemia on Muscle Protein.* Brit. J. Exper. Path. 29:121 (April), 1948.

The authors were interested in studying the possible changes in muscle proteins which might be produced by ischemia. For this purpose they determined the amino acid content of the gastrocnemius and adductores muscles of the albino rat. Muscle ischemia was produced by means of metal clamps applied to the hind limb of the intact animal under ether narcosis. The

results were compared with those obtained on autolytic muscle of rats which were sacrificed and allowed to remain in the same environmental conditions as the "clamped" rats.

The results indicated that proteolysis, as judged by an increase in amino acid content, occurred in muscle deprived of the major part of its blood supply. The amount was much greater in ischemic than in autolysing muscle, the difference being considered to be related to the higher temperature of ischemic muscle. For the first hour after removal of the clamp, proteolysis occurred at an even greater rate than during the period of ischemia. It was felt that this was due to the fact that at this time there was a further increase in temperature in the muscle while the pH was still low. The second phase of protein breakdown did not commence until about three days after the period of ischemia and continued for the next four days. The pH conditions at this time were not suitable for the action of the tissue cathepsins, and the enzymes producing this proteolysis were probably derived from the leucocytes which infiltrate the damaged muscle.

ABRAMSON.

Sziberth, K.: Endangiitis Obliterans: A Contraindication to Stomach Resection. Wien. med. Wchnschr. **98**:160 (April), 1948.

A 37-year-old man who had been subject to increasing intermittent epigastric pains for five years showed diminished pulsations in peripheral arteries and radiological signs of a duodenal ulcer. A stomach resection was carried out. However, on the day which followed the operation the patient died. Autopsy revealed the cause of death to have been multiple hemorrhagic infarctions of the small intestine on the basis of mesenteric endangiitis; the peripheral arteries and the left coronary artery showed similar changes. The symptomatology of this relatively rare picture, its diagnosis, and implications concerning surgical decisions are discussed.

BRUMLIK.

Lenegre, J., Kilaidonis P., and de Brux, J.: Calcification of the Ascending Aorta. Arch. d. mal. du coeur **41**:193 (May), 1948.

Of thirty cases with calcification of the ascending portion of the aorta, twenty were known to have syphilis although only nine were seropositive at the time of the examination. Calcified syphilitic aortitis is in general better tolerated than aortitis without calcification. The rigidity of the aorta does not seem to play a part in left ventricular failure in aortic lesions. Calcification of the aorta must be considered a valuable sign of syphilitic aortitis which has become stationary and nonprogressive.

HECHT.

Braham, J., and Howells, G.: Hereditary Oedema (Milroy's Disease). Brit. M. J. **2**:830 (May 1), 1948.

The author discusses Milroy's disease, which is characterized by edema which is usually present in infancy or childhood and always by adolescence. The edema usually begins in the foot but never extends above the inguinal ligament. At first it is of the pitting type but later it becomes brawny. It affects one or both lower limbs. There is no known successful treatment other than possibly the Kondoleon operation; however, this disease is compatible with a long, nondisabling life. The familial hereditary background is necessary for diagnosis, but possibly there are some cases seemingly without this requirement, as this characteristic may skip a generation. Extant material for pathological study is limited to one biopsy which showed condensation of the superficial dermal papillary layer with hyalinization.

The author describes the case of a nineteen-year-old boy who complained of a nondisabling swelling of the right leg which began at age seventeen. One sister was similarly affected. There were no trophic lesions. Laboratory examinations were normal. No treatment was advised other than elastic bandages.

WAGNER.

Kumpe, C. W., and Bean, W. B.: Aortic Stenosis: A Study of the Clinical and Pathologic Aspects of 107 Proved Cases. Medicine 27:139 (May), 1948.

The authors report the clinical and morphological aspects of 107 proved cases of aortic stenosis uncomplicated by deforming lesions of other valves. About three-fourths of the cases were men. A positive history of acute rheumatic fever was obtained in two-thirds of the cases. The cases were divided into two groups on the basis of symptoms and the course of the disease. Group 1 included those whose major complaints were related directly to the heart and those in congestive heart failure. Group 2 included those whose major complaints were not directly related to the heart. Of the seventy-eight patients in Group 1, thirty-four had chronic congestive failure, ten had intermittent bouts of failure, and nineteen had an abrupt onset of failure shortly before they were admitted. The blood pressure was not characteristic. There were a number with systolic hypertension and others with low diastolic pressures, but relatively few with the low systolic and the low pulse pressure described as typical of aortic stenosis. The second aortic sound was usually absent or much reduced in intensity. Occasionally a second sound heard at the aortic area was loud and must have been transmitted from the pulmonic valve. A systolic murmur was heard at the base in only 83 per cent of the patients, this murmur being transmitted into the vessels of the neck in slightly less than one-half of those in whom it was heard. Basal diastolic murmurs were heard in one-third of the patients. Apical systolic murmurs were heard in 82 per cent of the patients and an apical diastolic murmur was heard in slightly less than one-third. Thrills were felt in thirty-three patients. The systolic murmurs and thrills were related in intensity to the degree of stenosis, but they were absent in several cases of severe valvular obstruction. Fluoroscopic demonstration of calcified aortic valves verified the diagnosis five times. The electrocardiogram was not pathognomonic.

Cardiac pain occurred in 37 per cent of the patients before hospitalization and in 8 per cent while under observation. It differed from typical angina pectoris in its lack of radiation or its radiation to the right, its advent after, rather than during, exercise and its refractoriness to nitroglycerin. It was much more closely associated with severe aortic stenosis than with coronary arteriosclerosis.

The hospital course was characterized by signs of congestive failure unusually refractory to treatment with digitalis, oxygen, or diuretics. Episodes of sweating, cyanosis, restlessness, and confusion occurred in twenty-eight patients. Signs and symptoms referable to the brain were conspicuous in thirteen patients. The authors differentiated the type of sudden death which ended the life of 21 per cent of their patients from instant syncopal death and unexpected death where the terminal stage lasts for hours. In their material sudden death occurred in a matter of minutes, usually between five and thirty. In contradistinction to those with instant death following myocardial infarction, a history of syncopal attacks was not common in those bedfast patients who died suddenly.

The lesions of aortic stenosis were graded into three classes on the basis of severity. In every valve calcium was found grossly or histologically and it varied in quantity with the severity of the lesion. In severe lesions the coronary ostia were distorted. Fusion of cusps and nodule formation were common. The hearts were enlarged in the majority of cases and the heart weight was related to the extent of valvular obstruction. Coronary arteriosclerosis was common, and had given rise to thrombosis and myocardial infarction in an appreciable number of cases. The clinical diagnosis was made in only 24 per cent of all cases, reflecting both unfamiliarity with the diagnostic criteria and too great acceptance of the classic triad of basal systolic murmur, thrill, and small, slowly rising pulse.

KLINE.

McCall, M.: Dicumarol Therapy in Acute Coronary Occlusion With Myocardial Infarction. Am. J. M. Sc. 215:612 (June), 1948.

Dicumarol was used as the sole anticoagulant in the management of seventy-one patients with myocardial infarction following acute coronary occlusion. No effort was made to compile statistical data on these patients. Gross hematuria occurred on three occasions and was readily controlled by the intravenous administration of 60 mg. of menadione bisulfite. Unexplained

difficulty was encountered in the maintenance of the desired prothrombin time in twenty-(patients. Nine deaths in the group gave a mortality of 12.7 per cent. Six were due to he failure, and one each to rupture of the ventricle, pulmonary embolism, and extension of the farction. It is emphasized that a daily prothrombin determination is mandatory for success therapy. The author concludes that continued use of this form of therapy is justified by t resultant low incidence of thromboembolic phenomena, which insures a less stormy convalesce period.

DURAN

Reich, C., and Eisenmenger, W.: Further Studies on the Anticoagulants. Am. J. M Sc. 215:617 (June), 1948.

This report embodies a continuation of studies on Dicumarol and heparin initiated at Leno. Hill Hospital in 1943. In the present series of 300 cases, the patients were divided into four mai groups: (1) patients with postoperative cases treated prophylactically with anticoagulant to prevent thrombotic complications; (2) patients with active venous thrombosis; (3) patient with acute embolic episodes, usually pulmonary; and (4) patients with coronary thrombosis.

There were about 200 patients in the first group, at least 50 per cent being women who had had pelvic operations. The treatment in this group was with Dicumarol, which was started two to four days postoperatively and maintained until the patient was ambulatory. The results were most satisfactory, and it is possible to practically guarantee the prevention of postoperative thromboses in patients so treated. In the third group, there were thirty patients, twenty-six of whom had pulmonary emboli. Combined heparin and Dicumarol therapy was used. There were two deaths, and one other patient had a nonfatal pulmonary embolus while on anticoagulant therapy. As a result of experience in this group, it is suggested that if surgery is contemplated while a patient is on Dicumarol therapy, 120 mg. of vitamin K be injected intravenously a few hours preoperatively.

The second group included forty-five patients with thrombophlebitis, twenty of whom were postoperative patients who had received no preoperative anticoagulant treatment. Dicumarol was used without heparin in this group. In none of these patients were there any pulmonary emboli. When therapy is used promptly in this group the thrombosis can be restricted to just one segment of the vein and often the collateral circulation is sufficient to prevent lymphatic stasis.

In the fourth group there were thirty patients with coronary artery disease, twenty-four of whom were typical examples of coronary occlusion with myocardial infarction. Of these, four died; two of progressive failures, one after having shown clinical and electrocardiographic evidence of progressive myocardial damage, and one in what seemed to be a new acute coronary episode. While this group is too small to present any definite conclusions, the impression is given that the main usefulness of anticoagulant therapy in coronary artery disease is in the prevention of embolization either from peripheral veins or cardiac mural thrombi.

It is pointed out that there may be an increased sensitivity to Dicumarol in cases of congestive failure, possibly because of the decreased renal blood flow with retention of Dicumarol.

DURANT.

Starr, I., and Mayock, R. L.: On the Significance of Abnormal Forms of the Ballistocardiogram. A Study of 234 Cases With 40 Necropsies. Am. J. M. Sc. 215:631 (June), 1948.

The various types of abnormalities of ballistic form are described. The form may vary from beat to beat, or it may vary with respiration so that in many cases no one type of complex predominates. In other cases one type of abnormality does predominate, but there is usually some beat-to-beat variation.

Abnormalities of ballistic form were encountered most frequently in the cases in which there was manifold evidence of heart disease, or in conditions such as hypertension and hyperthyroidism in which heart disease is a frequent complication. They were found with great frequency in cases in which structural abnormalities of the heart were later demonstrated at necropsy. Never-

theless, ballistic abnormalities of form were encountered in fifty-eight cases in which no cardiac abnormality had been suspected and in eight cases in which the heart was essentially normal at necropsy.

It is concluded that an abnormality of ballistic form indicates an important type of cardiac dysfunction, the manifestation of an abnormal manner of contraction. This functional abnormality is usually associated with well-known kinds of structural abnormality, but it has also been found quite frequently when cardiac disease was not detected by the routine clinical tests now in use.

DURANT.

Tamagna, I. G., and Poindexter, C. A.: A Comparative Evaluation of Tetraethylammonium Chloride and Sodium Amytal in Patients With Hypertensive Cardiovascular Disease. Am. J. M. Sc. **215**:651 (June), 1948.

Tetraethyl ammonium chloride when compared with sodium amytal appears to be a safe and more specific agent for the preoperative evaluation of hypertensive patients. Results are obtained within thirty minutes, as compared to five hours with sodium amytal. The patient is awake throughout the test, whereas he is subjected to a day of drowsiness from sodium amytal. There is marked parallelism in the drop in blood pressure in both tests.

DURANT.

Soloff, L. A., and Bello, C. T.: "Capillary Fragility" in Hypertension: The Effect of Antiscorbutic Therapy on Results of Tests for "Capillary Fragility." Am. J. M. Sc. **215**:655 (June), 1948.

The capillary fragility of fifty hypertensive patients previously saturated with vitamin C for one month was determined by the Göthlin and Rumpel-Leede tests. Only two patients had a positive Göthlin test, while thirty-three had a positive Rumpel-Leede test. This is in contrast to the studies of Griffith and Lindauer in which 18 per cent of hypertensive patients were found to have a positive Göthlin test. The authors believe that the administration of vitamin C in their series may have prevented the appearance of a positive reaction to this test in most of their cases, and suggest the need for a re-evaluation of this test on a large series of patients previously saturated with this vitamin. They also suggest that the incidence of subclinical scurvy in hypertensive patients may be higher than in the group of normal students studied by Bell, Lazarus, and Munro.

The authors found that Rutin did not reverse to normal the Göthlin test of the two patients with abnormal reaction, nor did it reverse to normal the Rumpel-Leede test in the thirty-three patients with a positive reaction to this test. There did not appear to be any correlation between retinal hemorrhages and a positive Rumpel-Leede reaction.

DURANT.

Soloff, L. A., and Bello, C. T.: The Relationship of Retinal Hemorrhages in Hypertensive Patients to Cerebral Hemorrhage. A Comparison of the Retinal Picture in Hypertensive Individuals Who Died of Heart Failure With Those Who Suffered a Cerebral Hemorrhage. Am. J. M. Sc. **215**:660 (June), 1948.

Retinal hemorrhages occurred in fourteen (77 per cent) of eighteen patients with hypertension who died of cardiac failure without cerebral hemorrhage. They occurred in five (29 per cent) of seventeen patients with hypertension who suffered a cerebral hemorrhage. An analysis of the retinal picture found in the cases studied revealed the fact that a marked degree of spasm, usually with Grade 2 sclerosis, is necessary for the production of retinal hemorrhages. The spasm is apparently of importance in producing an extra burden on the heart or kidneys and thereby producing failure of either or both of these organs. Apparently, if this is not correctable, the patient does not live long enough to suffer a cerebral hemorrhage.

The study therefore indicates that retinal hemorrhages cannot be used as a prognostic sign of future cerebral hemorrhage, as they occur more frequently in those who ultimately die of cardiac or renal failure without a massive cerebral accident.

DURANT.

Unterman, D., and DeGraff, A. C.: The Effect of Exercise on the Electrocardiogram (Master "Two-Step" Test) in the Diagnosis of Coronary Insufficiency. Am. J. M. Sc. **215**:671 (June), 1948.

The Master "two-step" exercise test was performed in 163 subjects, including controls, patients with heart disease, and patients convalescing from acute illness. The electrocardiographic changes following exercise were regarded as significant in 40.7 per cent of fifty-nine patients with coronary disease and in 48.3 per cent of thirty-one patients with the anginal syndrome. No serious untoward reactions to exercise were noted. The electrocardiographic response was positive in seven of ten patients who experienced anginal manifestations during the test. A small number of patients with a negative "standard" test showed a positive test when the "double standard" exercise was performed.

The test provides a means of determining coronary insufficiency when other means are not available, although it does not do so in all cases. The practical value of the test appears to be limited by a high incidence of negative responses. The theoretical aspects of the test are discussed. The possible influence of different electrocardiographic techniques and criteria, as well as the influence of food, digitalis, and recent acute illness, is considered.

DURANT.

Bailey, W. H.: Air Embolus in Pneumoperitoneum. Report of a Fatal Case. Am. Rev. Tuberc. 57:621 (June), 1948.

The patient was admitted to the hospital with a diagnosis of pulmonary tuberculosis with endobronchial involvement. The initial pneumoperitoneum was instituted with no untoward results. The first refill, in which the air embolus occurred, took place twelve days later.

After twice verifying the fact that the point of the needle was in the peritoneal cavity the manometer tube was connected to the needle and a fluctuation of zero plus one was obtained. The air, flowing freely, was permitted to enter the peritoneal cavity under gravity. When 100 c.c. of air had been introduced, the reading was still zero plus one. The patient noticed no unusual reactions. Just when the 300 c.c. mark was reached, the patient stated that he felt dizzy. The needle was withdrawn; two seconds later the patient had a general convulsion and was given 1.0 c.c. of adrenalin. By this time the patient had lost consciousness, but respiration and pulse continued. He was given 2.0 c.c. of adrenalin intravenously, followed by artificial respiration and oxygen, and 5.0 c.c. of Coramine intravenously. The patient expired fifteen minutes after the refill was started and thirteen minutes after the onset of dizziness. Autopsy and microscopic examination of the internal organs failed to reveal the exact route of the air. On gross section of the heart, numerous small air bubbles were visible on the outer superior surface of the parietal pericardium. When the heart cavities were opened, a large quantity of frothy blood and stringy clot was found in the right auricle and ventricle. No air bubbles were found in the left side.

The author concludes that in inducing artificial pneumoperitoneum all technical details of injecting the air must be strictly followed. The injection should proceed very slowly at first, and the patient should be watched carefully. If the patient complains of any unusual sensations the injection should be stopped at once.

BELLET.

Wallis, A. D.: The Relation of the Cardiac Lesions of Rheumatoid Arthritis to Those of Rheumatic Fever. Ann. Rheumat. Dis. 7:97 (June), 1948.

It is the author's purpose to propose that in rheumatoid arthritis, cardiac lesions indistinguishable from those of rheumatic fever are produced by tissue response to the union of sessile antibody and fresh antigen, the latter being necessarily homologous to the sessile antibody but presumably different from the antigen in rheumatic fever. The mechanism of production of cardiac lesions is the same in the two diseases, but the antigens are different.

The *Streptococcus hemolyticus* is a causative factor in rheumatic fever but not in rheumatoid arthritis. The relation of scarlet fever and hemolytic streptococcic sore throat to acute rheumatic

fever and the prophylaxis of acute rheumatic fever by sulfonamides are well established. The extraordinary prolongation of the active stage of the joint lesions of rheumatoid arthritis, their tendency to symmetry, and their indifference to sulfanilamide and penicillin may be cited as evidence against a streptococcal etiology for this kind of arthritis. Whatever the substance eventually to be found serving as antigen in rheumatoid arthritis, the evidence indicates that it is not a streptococcal derivative.

In the cases reported by Baggenstoss and Rosenberg, rheumatic-type heart disease was found in the autopsy study of sixteen of twenty-two cases of frank rheumatoid arthritis, an incidence of 72 per cent as compared with the over-all incidence of five per cent found at the Mayo Clinic. I nonly two of these sixteen cases had a history of rheumatic fever been obtainable. It was noted tha t cardiac damage tends to be less severe in rheumatoid arthritis than in classical rheumatic fever and it is suggested that this difference might result from the fact that the onset of rheumatoid arthritis is later than the onset of rheumatic fever.

The concept of sensitivity reactions in rheumatoid arthritis also furnishes an explanation of the presence of focal collections of round cells in the peripheral nerves and skeletal muscles in this disease. It seems likely that these cell collections have the same origin as the cardiac lesions which are under discussion, namely, the result of union of fresh circulating antigen with homologous sessile antibody. Fresh antigen enters the circulation more frequently, over a longer period, and probably in smaller amounts in rheumatoid arthritis than in rheumatic fever, and also the "sensitivity lesions" are more likely to leave permanent recognizable scars in the heart than in the peripheral nerves.

BELLET.

Johnson, J., and Kirby, C. K.: The Surgical Treatment of the Infantile Type of Coarctation of the Aorta. Ann. Surg. 127:1119 (June), 1948.

The authors describe the two types of coarctation of the aorta. One is the adult type, which is short and occurs in the region of the ligamentum arteriosum; the other is the infantile type, which is long (4 to 5 cm.) and occurs in the region of the isthmus of the aorta. They point out that the adult type is effectively treated by resection of the stenotic area and restoration of continuity by end-to-end suture anastomosis, as described by Crafoord and Gross. However, the infantile type is not susceptible to an end-to-end anastomosis because of the long gap produced by the removal of the stenosed portion of the aorta. In three patients the authors were able to bridge this gap by using the left subclavian artery and carrying out an end-to-end anastomosis between it and the descending aorta.

The first patient, a 13-year-old boy, was restored to normal, whereas the second patient, a 17-year-old boy, was helped somewhat. The third patient, a 20-year-old man, died twelve hours after operation as a result of a rupture of the subclavian artery due to advanced arteriosclerotic changes in the vessel. The authors suggest that the ideal time to operate on these patients would be between the ages of 12 and 14 years.

LORD.

Samson, P. C.: Battle Wounds and Injuries of the Heart and Pericardium: Experiences in Forward Hospitals. Ann. Surg. 127:1127 (June), 1948.

Samson discusses the problems associated with the management in forward hospitals of cardiac injuries occurring during warfare. There were three chief types of injuries: contusion of the ventricular wall, laceration of the ventricle or auricle, and retained foreign bodies either in the muscle of the heart or within the chamber of the heart. Pericardial injuries consisted of foreign bodies, hemopericardium, and lacerations of the pericardium.

The author emphasizes many diagnostic features of cardiac injury; he points out that the most significant was the clinical picture of cardiac dysfunction (persistent dyspnea, tachycardia, arrhythmia, etc.), which was out of proportion to the patient's obvious injuries.

Samson states that contusions of the heart are nonsurgical and should be managed like coronary occlusion, in that surgical procedures for other injuries should be delayed if possible for at least forty-eight hours. Early operation on patients with a contusion of the heart usually ended

fatally. Lacerations of the heart should be sutured if the patient's condition warrants and the pericardium drained into the left pleural space. In general, foreign bodies in the pericardium, in the myocardium, or in the chambers of the heart should be removed, but the mortality is considerably less if the operation can be postponed until the patient returns to a base hospital. Occasionally a foreign body embolus caused injury to the myocardium so that early surgical intervention was necessary.

The author discusses several points in regard to surgical technique which had proved to be of value in the management of cardiac injuries.

LORD.

Scott, M. R. A.: Weight and Blood Pressure. Brit. M. J. 2:1195 (June 19), 1948.

A review of weights and blood pressures of an office staff, all men, was undertaken. This staff numbered 1,200 in 1938, 400 in 1943, and 600 in 1946. The group was examined in 1938-1939, 1943, and 1946-1947. The average age of the group varied considerably at different examinations: in 1938 the largest number was in the twenty six- to forty-year group, while in 1946, the sixteen- to twenty-year group was largest. The average weight in 1938 was 155 pounds, fully clothed; in 1943 it fell to 151 pounds and rose to 156 pounds in 1946.

It was found that up to the age of 40 years, men examined in 1946-1947 were on the average heavier than men of the same age in 1938-1939. In men from 41 to 55 years of age there was little difference in weight in the two periods. The men between 21 and 35 years who had been in the Armed Forces were on the average heavier than those who had not been.

The average diastolic pressures of all age groups in 1946-1947 were above those of 1938-1939, the maximum difference being 12 mm. Hg in the group between 41 and 45 years of age. Diastolic pressures were highest in 1943, probably reflecting war-produced anxiety. The average systolic pressures of all age groups in 1946-1947 were above those of 1938-1939, the maximum difference being 27 mm. Hg in those between 46 and 50 years of age. The rise in blood pressure can be correlated with a recent increase in neurocirculatory disorders in the staff over 50 years of age.

WAGNER.

Handelsman, J. C., Bing, R. J., Campbell, J. A., and Griswold, H. E.: Physiological Studies in Congenital Heart Disease. V. The Circulation in Patients With Isolated Septal Defects. Bull. Johns Hopkins Hosp. 82:615 (June), 1948.

The authors report five cases with various types of septal defects and discuss the underlying physiologic principles relating to and the methods used in eliciting the disturbances observed in these conditions. The Fick principle was applied to determine the blood flow through various parts of the circulation. The following formulas were used:

$$\text{Systemic blood flow (ml. per minute)} = \frac{O_2 \text{ uptake (ml. per minute)} \times 100}{O_2 \text{ content of peripheral arterial blood (volumes per cent)} - O_2 \text{ content right auricular blood (volumes per cent)}}$$

$$\text{Pulmonary artery flow (ml. per minute)} = \frac{O_2 \text{ uptake (ml. per minute)} \times 100}{O_2 \text{ content of pulmonary vein blood (volumes per cent)} - O_2 \text{ content pulmonary arterial blood (volumes per cent)}}$$

$$\text{Shunt (ml. per minute) right-to-left} = \text{systemic flow} - \text{pulmonary artery flow}$$

$$\text{Shunt (ml. per minute) left-to-right} = \text{pulmonary artery flow} - \text{systemic flow}$$

The calculation of systemic flow was complicated by reciprocal admixture through an auricular septal defect. This necessitated the use of the oxygen content of blood from the superior vena cava as representative of mixed venous blood. This may provide an error in the results, since it has been shown that true mixture of venous blood does not occur before the outflow tract of the right ventricle.

As part of the physiological studies conducted in this group, three of the patients performed the standard exercise test. In all, there was a rise in the oxygen consumed per liter of ventilation. This finding is in contrast to the results obtained in the study of patients with the tetralogy of Fallot. In these latter there was generally a fall in the ratio of oxygen consumed per liter of ventilation during exercise. Conversely, in the present group under study, as in normal individuals and in patients with Eisenmenger complex, the rise in oxygen consumed per liter of ventilation during exercise demonstrated that the effective pulmonic blood flow can increase significantly with exercise.

Three patients had shunts from left to right and two had right- to left-shunts. In these two latter patients cyanosis was marked and the oxygen saturation of the peripheral arterial blood was low.

Pulmonary factors concerned with oxygen transfer in the lung are apparently not involved in this decrease in the saturation of peripheral arterial blood. In sixteen patients in whom it was possible to catheterize the pulmonary vein, the blood returning to the heart from the lungs was fully saturated. The finding, in two of these cases, that the shunt was predominantly directed to the left, implies an increase in the resistance of the pulmonary vascular tree. Evidence of increased resistance in the pulmonary vascular circuit is furnished by four findings: (1) intracardiac shunting of blood from right to left; (2) the presence of pulmonary arterial hypertension; (3) the marked loss of pressure head in the pulmonary circulation which became apparent when resistance in the pulmonary circuit was calculated; and (4) the changes in the ratio, velocity energy/total work, of the two ventricles.

In the light of the observation that normally pulmonary resistance is low, the assumption may be ventured that the increase in pulmonary resistance results from changes in the pulmonary vascular tree in the form of widespread sclerotic changes affecting the smaller blood vessels possibly in combination with thrombi. However, it is impossible to state at this time whether or not such changes are a result of increased pulmonary artery flow or develop as a result of other factors; in some cases rises in left intra-auricular pressure may be the cause for the increased pulmonary resistance.

BELLET.

Loewe, L., Hirsch, E., Grayzel, D. M., and Kashdan, F.: Experimental Study of the Comparative Action of Heparin and Dicumarol on the In Vivo Clot. J. Lab. & Clin. Med. 33:721 (June), 1948.

Clotting was induced in the jugular veins of adult rabbits. Nine to fourteen days after the induction of thrombosis, heparin and Dicumarol were administered to alternate animals. Sufficient amounts of anticoagulant were given to maintain either the coagulation time or the prothrombin time well above clinically accepted limits. The anticoagulants were administered for two weeks.

The authors found that in the presence of heparin all clots underwent resolution if they were in the sludge stage. Dicumarol did not produce this response because of the time lag between the administration of the drug and the effective prolongation of the prothrombin time. However, beyond this initial stage, both anticoagulants effectively caused resumption of clinical patency in a considerable number of veins which were occluded by clots for four days or longer, even up to two weeks. This effect is at variance with the commonly accepted knowledge of thrombus behavior. The degree of recanalization appears to be greater with heparin. On the basis of this comparative study it would appear that heparin is superior to Dicumarol as an anticoagulant agent.

KLINE.

Horlick, L., and Katz, L. N.: The Effect of Diethylstilbestrol on Blood Lipids and the Development of Atherosclerosis in Chickens on a Normal and Low Fat Diet. J. Lab. & Clin. Med. 33:733 (June), 1948.

The implantation of stilbestrol pellets in young chickens resulted in a marked hyperlipemia and hypercholesterolemia while on a normal diet and on a specially prepared low fat diet. After stilbestrol implantation, chickens on the normal diet developed a somewhat higher cholesterolemia than did the chickens on the low fat diet. Atherosclerosis of the induced type was observed in a high proportion of the stilbestrol-treated chickens in both the group receiving the normal diet and the group receiving the low fat diet. Spontaneous atherosclerosis occurred in 40 per cent of the chickens used as normal controls, but it occurred in none of the control group which was placed on a low fat diet. The authors state that stilbestrol probably acts to produce atherosclerosis through its cholesterolemic effect.

KLINE.

Slaughter, O. L., Brown, H. S., and Wakim, K. G.: Effects of Tetraethylammonium Chloride on Blood Flow in the Extremities of Man. J. Lab. & Clin. Med. 33:743 (June), 1948.

The purpose of this study was to determine the effect of tetraethylammonium chloride on the blood flow in the upper and lower extremities of healthy human subjects exposed to relatively warm environment (temperature ranging between 80° and 85° F.) and to establish a basis for comparison with subsequent studies on various abnormalities of the vascular system in patients.

Tetraethylammonium chloride was given intravenously to seven healthy adults. The effects of the drug were studied plethysmographically by the use of the compensating spirometer recorder. In the presence of vasodilatation due to a relatively warm environment of 80° to 85° F., tetraethylammonium chloride produced an average increase in blood flow of 100 per cent in the forearms and 135 per cent in the legs. In addition to the increase in blood flow, disturbances of vision with impairment of accommodation, metallic taste and dryness of the mouth, and increase in heart rate occurred after injection of tetraethylammonium chloride.

KLINE.

Fastier, F. N., and Smirk, F. H.: Some Properties of Amarin, With Special Reference to Its Use in Conjunction With Adrenaline for the Production of Idio-ventricular Rhythms. J. Physiol. 107:318 (June), 1948.

The circulatory effects of Amarin, a cyclic amidine derivative, were studied in dogs by a number of mechanical devices, including motion pictures, electrograms, myocardiographs, oscillography, etc., and by direct observation. This compound causes a profound bradycardia with lengthening of the P-R and QRS-T durations, occasionally to three times the normal, by a nonvagal effect. In larger doses the heart beat may originate from the A-V node or from a ventricular focus. Various types and degrees of heart block were noted, as were such abnormalities as the independent contraction of the auricles, the driving of the auricles by the ventricles, electrical alternation, and changes in S-T segment and T waves. Small doses exert a pressor action by peripheral vasoconstriction. Larger doses may produce circulatory collapse with cardiac dilatation and arrest.

After Amarin the pressor responses to small doses of epinephrine are greatly increased in the anesthetized animal. Ventricular flutter could be readily produced by moderate doses of epinephrine. When this was observed directly, a series of peristalsis-like waves succeeded each other over approximately the same course on the ventricular surface; two or three waves could be seen at one time and these did not originate from any single point. It would seem that the refractory period was shortened, and flutter would develop after a new excitatory wave began before the preceding ventricular wave had ended. Just before flutter develops, one may see an R wave superimposed on a T wave. This is probably an extreme instance of an increase in duration of ventricular systole relative to that of diastole.

Under Amarin, ventricular fibrillation appeared as many small wavelets running in different directions. Many regions of the ventricles showed regular cycles of mechanical movement which

were not necessarily repeated in the same direction, nor were they of equal strength. Thus, ventricular fibrillation, under these conditions, did not appear to depend on any simple system of circus rhythms. Flutter induced by Amarin and epinephrine was probably due to multiple circus rhythms.

WAIFE.

Konzett, H., and Verney, E. B.: Observations on the Urine, Blood and Arterial Pressure of Dogs Before and After the Production of Renal Ischemia. J. Physiol. 107:336 (June), 1948.

These investigators were unable to confirm the report of Lockett (J. Physiol. 105:126, 1946) that a new base, termed x, was present in the urine of dogs after the production of renal ischemia. Lockett claimed that this base is absent in normal animals, that it appears in the urine within ten minutes following renal artery compression, that it is excreted mainly by the normal renal cortex, and that a clear relation exists between the presence of this substance and hypertension. On the contrary, these authors found that a color test for the x substance was positive in normal urine, and no increase was noted after renal artery obstruction. Piperidine in the dog's urine gives the same color reaction as the postulated x substance.

WAIFE.

Ogilvie, T. A., Penfold, J. B., and Clendon, D. R. T.: Gangrene Following Intra-arterial Injection of Myanesin. Lancet 254:947 (June 19), 1948.

A 67-year-old woman was admitted to the hospital with a provisional diagnosis of neoplasm of the stomach. Laparotomy revealed a gall bladder with thickened walls surrounded by many adhesions and cholecystectomy was performed. During the operation 10 ml. of 10 per cent Myanesin was injected into the median basilic vein to obtain muscular relaxation. The same day the right forearm and hand were much discolored, deeply cyanosed, and of marble coldness; but a good radial pulse was easily palpable at the wrist. A brachial plexus block was performed with procaine, but the circulation did not improve. Next day the hand and forearm were still blue, cold, and functionless, although there was a good radial pulse. A cervical sympathetic block was done, but though the fingers may have been slightly warmer for a short time, after this procedure they were still deeply cyanosed.

Two days later the arm was blue, cyanosed, and cold from the finger tips to the elbow, the nails being almost black. The brachial artery was exposed opposite the elbow joint; the wound bled freely above the elbow, but did not bleed below the joint level, and the superficial veins were collapsed. No thrombosis was present in the brachial, radial, or ulnar artery. The gangrene of the hand and forearm progressed, but the patient's general condition gave no cause for anxiety. The arm was amputated three inches above the elbow joint. The upper end of the brachial artery showed unorganized ante-mortem thrombus attached to the intima.

Subsequent experimental studies revealed that the curdling observed was not due to the effect of Myanesin on the blood, plasma, serum, or heparin, but that there was an alteration in the physical state of the Myanesin with its subsequent precipitation from solution by some constituent or constituents of the blood. It is possible, therefore, that the gangrene in this case can be explained by the profound change which takes place when blood and Myanesin are mixed.

It is possible that, in spite of adequate skill and care in making the injection, some of the solution was injected into the brachial artery instead of into the median basilic vein.

BELLET.

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BELLET.

Through this educational activity, the pharmacist will receive essential information concerning the heart diseases. As adviser to persons who see him before consulting their physicians, he will have better information whenever inquiries from the public reveal possible symptoms of heart disease. This will facilitate early referral of patients.

The bimonthly bulletins will be designed for posting in the prescription room. Each mailing will include a display card addressed to laymen. The cards will be informational in character and carry a "see your doctor" message to approximately 3,000,000 people who visit the pharmacists cooperating in this project.

The program calls for wide educational publicity in pharmaceutical journals, and for radio scripts and transcriptions for the use of local and state pharmaceutical associations. The American Heart Association will be consulted in the planning of the project and the preparation of all educational materials.

PROCEDURE FOR AFFILIATION OF LOCAL AND STATE ASSOCIATIONS

It is recommended that local or state Associations observe the following procedure in requesting affiliation with the American Heart Association:

1. Forward a letter to the American Heart Association acknowledging that the affiliate intends to abide by the formula for affiliation, as outlined by the American Heart Association.

The listing in that letter of the duly elected officers and the signing of that letter of application by two of those officers.

Specific description of the area of operation also to be included in this letter.

2. The submission of Statement of Purposes and By-Laws.
3. Submission of tentative budget and plan of operation for the succeeding year.
4. Nominations for the Assembly. Notify the President or other responsible officer that his affiliated Heart Association is entitled to a specified number of delegates to the Annual Assembly and that he is requested to make suggestions for nominations and send it out to us for reference to the Nominating Committee.

PROGRAM

TWENTY-SECOND SCIENTIFIC SESSIONS

AMERICAN HEART ASSOCIATION

June 3, 4, 1949

Vernon Room, Haddon Hall, Atlantic City, N. J.

FIRST SESSION

Friday, June 3, 1:30 p.m.

Chairman: Norman E. Freeman, Chairman, Section on Circulation
Secretary: Grace M. Roth

1. THE EFFECTS OF DIHYDROERGOCORNINE ON THE GENERAL CIRCULATION OF HYPERTENSIVE AND NORMOTENSIVE SUBJECTS. Joseph H. Hafkenschiel, Charles W. Crumpton, John H. Meyer, and William A. Jeffers, Philadelphia, Pa.
2. SYMPATHETIC VENOCONSTRICTOR REFLEXES IN MAN. Julius Litter and Robert W. Wilkins, Boston, Mass.
3. STUDIES OF THE PULMONARY AND SYSTEMIC ARTERIAL PRESSURE IN CASES OF PATENT DUCTUS ARTERIOSUS WITH SPECIAL REFERENCE TO EFFECTS OF SURGICAL LIGATION. B. E. Taylor, A. A. Pollack, H. B. Burchell, O. T. Clagett, and E. H. Wood, Rochester, Minn.

4. GEORGE BROWN MEMORIAL LECTURE. Walter H. Seegers, Wayne Universi College of Medicine, Detroit, Mich.
5. SYNTHETIC RATIONS IN THE STUDY OF DIETARY FACTORS IN EXPEI MENTAL RENAL HYPERTENSION IN THE RAT. Philip Handler and F. Ber heim, Durham, N. C.
6. ARTERIOSCLEROSIS AND PYRIDOXINE DEFICIENCY. J. F. Rinehart a L. D. Greenberg, San Francisco, Calif.
7. RELATIONSHIP BETWEEN PROTHROMBIN TIME AND PLASMA LEVELS (DICUMAROL. Murray Weiner, Shepard Shapiro, Julius Axelrod, and Bernai B. Brodie, New York, N. Y.
8. EPINEPHRINE AND NOR-EPINEPHRINE IN PHEOCHROMOCYTOMA. Marci Goldenberg and Henry Aranow, Jr., New York, N. Y.
9. HEPATO-RENAL VASOTROPIC FACTORS IN ESSENTIAL HYPERTENSION AN IN ECLAMPSIA. Ephraim Shorr and Benjamin W. Zweifach, New York, N. Y.
10. THE MECHANISM OF SOME ANTIDIURETIC RESPONSES AND THEIR RE LATIONSHIP TO THE SODIUM RETENTION OF CONGESTIVE CARDIAC FAII URE. B. C. Sinclair-Smith, J. H. Sisson, A. Genecin, A. Kattus, C. Monge, an E. V. Newman, Baltimore, Md.
11. THE EFFECT OF DIGOXIN IN LEFT VENTRICULAR FAILURE. M. Iren Ferrer, Rejane M. Harvey, Richard T. Cathcart, Andre Cournand, and Dickinso W. Richards, Jr., New York, N. Y.

SECOND SESSION

Saturday, June 4, 9:00 A.M.

Chairman: Tinsley R. Harrison, President, American Heart Association

Secretary: John J. Sampson

12. THE TREATMENT OF COARCTATION OF THE AORTA. Robert E. Gross, Boston, Mass.
13. COMMISSUROTOMY FOR MITRAL STENOSIS. Charles P. Bailey, Robert P. Glover, and Thomas J. O'Neill, Philadelphia, Pa.
14. THE NATURE AND TREATMENT OF AURICULAR FLUTTER. Myron Prinzmetal, Eliot Corday, Alvin L. Sellers, Walter A. Flieg, and H. E. Kruger, Los Angeles, Calif.
15. CATHETERIZATION OF THE LEFT HEART IN MAN. Henry A. Zimmerman, Roy W. Scott, and Norman O. Becker, Cleveland, Ohio.
16. THE VECTORAL INTERPRETATION OF PRECORDIAL T-WAVE INVERSION. Robert P. Grant, Atlanta, Ga.
17. QRS-T PATTERNS IN THE PRECORDIAL LEADS THAT MAY BE MISTAKEN FOR MYOCARDIAL INFARCTION. Gordon B. Myers, Detroit, Mich.
18. THE SYNDROME OF ACUTE MYOCARDIAL INFARCTION ASSOCIATED WITH EARLY ELECTROCARDIOGRAPHIC FINDINGS SUGGESTIVE OF PREDOMINANTLY SUBENDOCARDIAL INJURY, WITH OBSERVATIONS ON THE "TOUCH EFFECT" OF THE CARDIAC CATHETER. Hans H. Hecht, Leonard W. Ritzmann, and Marguerite Greaves, Salt Lake City, Utah.
19. THE SUBCUTANEOUS USE OF THIOMERIN, A NEW MERCURIAL DIURETIC FOR TREATMENT OF CONGESTIVE HEART FAILURE. Robert G. Batterman, David Unterman, and Arthur C. De Graff, New York N. Y.

Saturday, June 4, 12:00 P.M.

Annual Business Meeting of Members

THIRD SESSION

Saturday, June 4

Panel Discussions

Chairman: Eugene A. Stead, Jr., Chairman, Program Committee

1:30 P.M.

1. MANAGEMENT OF CONGESTIVE FAILURE AND IMPORTANCE OF LOW SODIUM DIET.

George E. Burch, New Orleans, *Chairman*
William Dock, New York
Walter Kempner, Durham
Samuel Proger, Boston
Ferdinand Schemm, Great Falls
James Warren, Atlanta

2:35 P.M.

2. CONGENITAL HEART DISEASE.

Alfred Blalock, Baltimore, *Chairman*
Richard Bing, Baltimore
Louis E. Martin, Los Angeles
Edward Neuhauser, Boston
Helen Taussig, Baltimore

3:40 P.M.

3. ANTICOAGULANT THERAPY.

Edgar V. Allen, Rochester, *Chairman*
Louis N. Katz, Chicago
I. S. Ravdin, Philadelphia
Walter H. Seegers, Detroit
Geza de Takats, Chicago
Irving S. Wright, New York

You are invited to forward a question or topic which you would like to have discussed at any of these panels to the American Heart Association, 1775 Broadway, New York 19, N. Y.

Saturday, June 4, 7:00 P.M.

ANNUAL DINNER

VERNON ROOM, HADDON HALL

PROGRAM COMMITTEE

Chairman: Eugene A. Stead, Jr., Durham

Graham Asher, Kansas City
James A. Greene, Houston
John Hepburn, Toronto
Louis N. Katz, Chicago
Robert L. King, Seattle
William G. Leaman, Jr., Philadelphia
Robert Bruce Logue, Atlanta
Louis E. Martin, Los Angeles
Benedict Massell, Boston
Hugh Montgomery, Philadelphia
Robert M. Moore, Indianapolis
Francis F. Schwentker, Baltimore
Roy W. Scott, Cleveland
Arthur P. Selzer, San Francisco
Morse J. Shapiro, Minneapolis
F. Janney Smith, Detroit
Harold J. Stewart, New York

INTERIM CAMPAIGN REPORT

Local affiliates and committees have reported campaign collections of approximately $2,100,000, as of March 21, 1949. This figure represents incomplete returns from 157 groups. Reports from 204 groups have yet to be received.

Of this amount, more than $100,000 was received at National Headquarters of the American Heart Association as the result of national radio and newspaper publicity, activity of cooperating service groups and fraternal organizations, and the distribution of plastic hearts and Save-a-Heart banks. Only a small fraction of plastic hearts and banks have been returned to National Headquarters. A considerable return is expected from these sources, especially the plastic hearts which average more than $6.25 per heart.

Final figures on the results of the 1949 campaign are not expected until May or June of this year. Complete reports from local groups will not be available for several months, and it would be premature to estimate the total national collection at this time.

It is of interest that a total of more than 7,000,000 pieces of printed literature were ordered; over 240,000 plastic hearts and 1,260,000 Save-a-Heart banks were distributed by the end of the campaign period.

A significant feature of the drive has been the rapid growth of committees in local areas. Enlistments of Campaign Chairmen and Co-chairmen increased from 174 on January 29 to 743 by the end of the campaign.

American Heart Journal

VOL. 37 JUNE, 1949 No. 7

Original Communications

INFLUENCE OF SODIUM CHLORIDE UPON THE ACTIONS OF DESOXYCORTICOSTERONE ACETATE

HANS SELYE, M.D., HELEN STONE, B.SC., PAOLA S. TIMIRAS, M.D., AND CARLOS SCHAFFENBURG, M.D.
MONTREAL, CANADA

IN PREVIOUS publications from this Institute attention has repeatedly been called to the fact that many of the toxic actions of desoxycorticosterone acetate (DCA) are dependent upon the sodium chloride content of the diet.[1,2,3] Thus, it has been shown that excessive dietary supplements of sodium chloride increase the severity of the nephrosclerosis, periarteritis nodosa, and hypertension produced by desoxycorticosterone acetate treatment, while diets which were comparatively poor in sodium chloride tend to diminish these toxic actions of this corticoid compound.

Extensive experimental work supports the view that in sodium chloride it is the sodium ion which is of importance in this connection. A variety of "acidifying salts," such as ammonium chloride, ammonium nitrate, calcium chloride, and others, also counteract the toxicity of desoxycorticosterone acetate presumably because these salts occasion severe losses of sodium.[4]

It is believed that the typical morphologic lesions produced by overdosage of desoxycorticosterone acetate in the presence of sodium are fundamentally due to a derangement in the deposition of hyalin ("fibrinoid") material. The characteristic hyalinization of arterioles and renal glomeruli, the formation of granulomatous nodules around hyalin plaques in the heart, and the deposition of fibrinoid material on the cardiac valves, the pericardium, the internal surface of blood vessels, and on other tissues form a syndrome which might well

From the Institut de Mèdecine et de Chirurgie expèrimentales, Universitè de Montrèal, Montreal, Canada.

This investigation was supported by the Commonwealth Fund of New York and by a research grant from the Division of Research Grants and Fellowships of the National Institute of Health, United States Public Health Service.

be described as "fibrinoid diathesis" or "hyalinosis," just as we speak of lipoidosis, calcinosis, or amyloidosis when excessive lipid, calcium, or amyloid deposition occurs throughout the body. This experimental "hyalinosis" caused by desoxycorticosterone acetate probably has its counterparts in human pathology in the form of such diseases as malignant nephrosclerosis, rheumatic arteritis, Libman-Sacks disease, diffuse collagen disease, periarteritis nodosa, thromboangiitis obliterans, and malignant arteriolosclerosis.

In this communication we wish to report upon an additional series of observations on rats receiving desoxycorticosterone while on a diet completely devoid of sodium chloride. Through such experiments we hoped to determine whether the dietary protection against desoxycorticosterone acetate is absolute or relative and whether it extends to all of the actions of this corticoid or is limited to some of them.

MATERIAL AND METHODS

Twenty-six female hooded rats weighing 90 to 110 grams (average 95 grams) were unilaterally nephrectomized and separated into two groups. The

TABLE I. COMPOSITION OF THE BASIC SYNTHETIC DIET (PARTS PER CENT)

Casein	20.0
Corn starch	73.0
Fat (Mazola)	1.0
Cod liver oil	1.0
Cellu flour	1.0
Na- and Cl-free mineral mixture	3.5
Vitamin supplements	0.5
Na- and Cl-free Mineral Mixture	*Grams*
(3.5 Gm. per 100 Gm. of diet)	
$MgSO_4.7\ H_2O$	24.6
K_2HPO_4	83.8*
$CaHPO_4.2\ H_2O$	69.8
Ca lactate.5 H_2O	15.4
Fe citrate	1.2
KI	0.16
Vitamin Supplements	
(0.5 Gm. per 100 Gm. of diet)	
Thiamine chloride	0.8
Riboflavin	0.8
Pyridoxine	0.8
Calcium pantothenate	1.5
Nicotinic acid	1.5
Choline chloride	400.0
Inositol	100.0
Para-aminobenzoic acid	30.0

*The usual 14.2 per cent of disodium hydrogen phosphate was replaced by an equivalent amount of dipotassium hydrogen phosphate.

rats in Group A acted as untreated controls, while in each animal of Group B two 40 mg. pellets of desoxycorticosterone acetate were implanted. All animals were given a synthetic diet containing 20 per cent "Labco" casein and a modification of the mineral mixture of Steenbock and Nelson,[6] in which the sodium chloride was eliminated and disodium hydrogen phosphate was replaced by an equivalent amount of dipotassium hydrogen phosphate in order to make the diet sodium chloride free (Table I). Distilled water was given as drinking fluid.

At the end of four weeks the blood pressures were determined by cannulation of a carotid artery and the animals were separated into four groups; six of the rats in Group A remained on the sodium- and chloride-free diet and distilled water (Group 1); the other six animals were kept on the same diet but were given 1.0 per cent saline to drink (Group 3). In the same manner, seven animals of Group B remained on the sodium- and chloride-free diet and distilled water (Group 2) and the other seven rats were given 1.0 per cent saline (Group 4). Two additional 40 mg. pellets were implanted at this time in the animals of Groups 2 and 4. Treatment was then continued for five more weeks, at the end of which time the moribund condition of the animals in Group 4 made it necessary to terminate the experiment. The blood pressures were again taken; then all the animals were killed and their organs weighed after fixation in "Suza" solution.

RESULTS

Table II summarizes our results. In the fourth column of this table the initial body weight represents the average weight of the animals after four weeks of treatment, when Group A was separated into Groups 1 and 3 and Group B into Groups 2 and 4.

The weight of the *kidney* is listed both in absolute terms and as a percentage of body surface. According to either manner of expression it was by far hi?hest in the rats treated with desoxycorticosterone acetate and receiving sodium chloride. This renal enlargement is typical of the early stages of nephrosclerosis before secondary contraction occurs. Sodium chloride deficiency (Group 1) can be seen to have caused some renal atrophy when the control animals on diets containing sodium chloride (Group 3) are compared. It is especially noteworthy that animals on a sodium chloride-free diet, even when treated with desoxycorticosterone acetate (Group 2) showed no increase in renal weight in comparison with the corresponding rats whose sodium chloride was depleted but which were not treated with desoxycorticosterone acetate (Group 1).

The degree of nephrosclerosis was expressed in a scale ranging from 0 to 3 plus; hence, the theoretic maximum of 3 plus was considered as equivalent to 100 per cent. It will be noted that when so expressed, the degree of nephrosclerosis caused by desoxycorticosterone acetate in rats on the sodium chloride-containing diet (Group 4) was 93 per cent, while not even the slightest microscopic trace of such a lesion was detectable in the rats with depleted sodium chloride (Group 2) which received the same amount of desoxycorticosterone acetate. (Figs. 1-4).

TABLE II. INFLUENCE OF NaCl UPON THE ACTIONS OF DESOXYCORTICOSTERONE ACETATE (MEANS AND STANDARD ERRORS)

GROUP	TREATMENT	DIET	BODY WEIGHT (GM.)		KIDNEY			HEART			BLOOD PRESSURE (MM. Hg)		ADRENAL (MG.)	HYPO-PHYSIS (MG.)	THYMUS (MG.)	Na IN PLASMA (m. eq./l)
			INITIAL	FINAL	MG.	MG/100 CM²B.S.	NEPHROSCLEROSIS (PER CENT)	MG.	PERCENTAGE BODY WEIGHT	MYOCARDITIS (PER CENT)	4 WEEKS	9 WEEKS				
1	Controls	Na+ Cl free	130 ±3	154 ±3	680 ±24	261 ±10	0	517 ±30	0.33 ±0.02	0	121 ±5	132 ±7	32 ±2	8 ±.06	179 ±34	127.5 ±2.46
2	Desoxycorticosterone acetate	Na+ Cl free	135 ±6	152 ±7	663 ±29	257 ±6	0	465 ±30	0.30 ±0.02	0	137 ±3	133 ±2	23 ±1	6. ±.04	188 ±23	130.4 ±1.28
3	Controls	Na+Cl free + 1%NaCl	130 ±7	165 ±8	900 ±75	329 ±17	0	616 ±24	0.37 ±0.005	0	122 ±3	132 ±5	41 ±4	8 ±.06	245 ±28	137.8 ±2.56
4	Desoxycorticosterone acetate	Na+ Cl free +1% NaCl	135 ±5	144 ±5	1195 ±75	483 ±39	93	674 ±11	0.47 ±0.02	53	120 ±3	154*	33 ±2	6 ±.04	58 ±10	171.3 ±10.4

*See text.

Fig. 1.

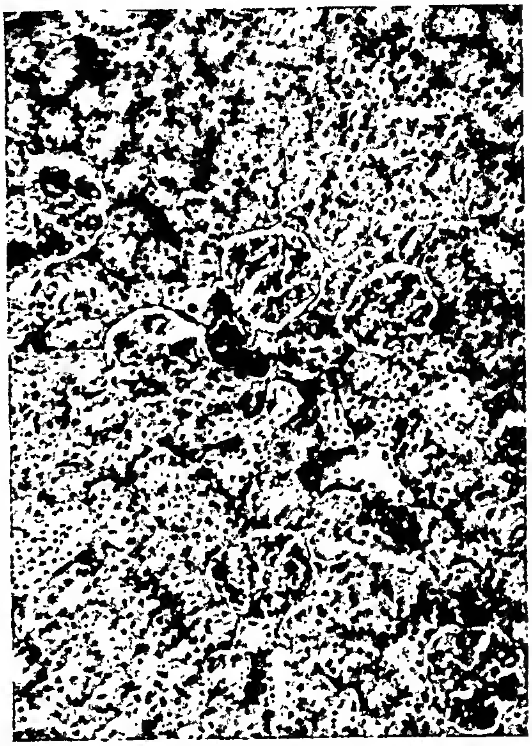

Fig. 2.

Fig. 1.—Nephrosclerotic kidney of a rat treated with desoxycorticosterone acetate and sodium chloride. Note hyalinized glomerulus and many dilated tubules, some of which contain hyalin casts (low magnification).

Fig. 2.—Normal appearance of the kidney of a rat which received the same amount of desoxycorticosterone acetate as the rat whose kidney is shown in Fig. 1, but which was kept on a sodium chloride-free diet (same magnification as Fig. 1).

Fig. 3.

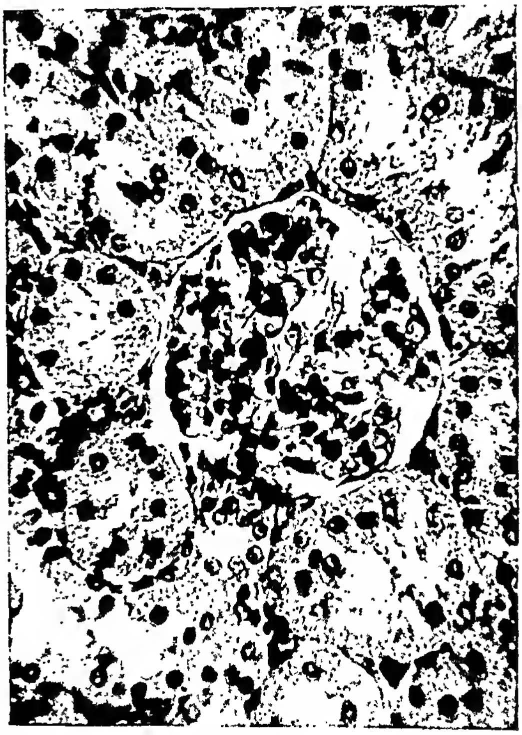

Fig. 4.

Fig. 3.—High magnification of a glomerulus from the kidney shown in Fig. 1. Note hyalin thrombi in several glomerular capillaries and protein precipitate in capsular space.

Fig. 4.—Normal glomerulus from the kidney shown in Fig. 2. Note that in the absence of dietary sodium, desoxycorticosterone acetate failed to cause glomerular hyalinization.

The *heart* weight is expressed both in milligrams and as a percentage of body weight. It will be noted that desoxycorticosterone acetate caused no significant increase in cardiac weight in the sodium chloride-depleted animals of Group 2. In fact, this substance appears to have produced a decrease, but this may not be significant. On the other hand, according to either manner of expression, the rats receiving desoxycorticosterone acetate on a diet containing sodium chloride (Group 4) had a significantly higher cardiac weight than the corresponding controls (Group 3). It should be emphasized that the heart weight is a rather reliable indicator of the mean blood pressure during the entire experimental period. Indeed, some investigators believe that this is a more accurate index of hypertension than the occasional actual measurement of blood pressure at intervals throughout the experiment, because it is less likely to be influenced by sudden transient variations.

Myocardial changes, with the formation of granulomas containing giant cells and hyalin deposits between the cardiac muscle cells, have been produced by desoxycorticosterone acetate only in animals on the diet containing sodium chloride (Group 4).

Although not specifically mentioned in the table, it may be stated that *periarteritis* of the mesenteric vessels likewise occurred only under the influence of desoxycorticosterone plus dietary sodium chloride (Group 4).

The *blood pressure* was measured after four weeks of desoxycorticosterone treatment, that is to say, when the animals of all four groups were still on a completely sodium chloride-free diet. At this time the mean blood pressure, determined under light ether anesthesia by direct cannulation of the carotid artery, was within normal limits in all four groups. Previous experiments had shown that after four weeks of treatment with desoxycorticosterone acetate, the blood pressure would have risen far above normal in rats receiving normal diets containing sodium chloride. After nine weeks, that is to say, five weeks after Groups 3 and 4 had been placed on sodium chloride, the blood pressure remained within normal limits in all rats except in those receiving both desoxycorticosterone and sodium chloride (Group 4). Some of these animals had subnormal blood pressures because they were practically moribund by this time. However, the sole representative of this group which was still in good condition had a mean blood pressure of 154 mm. Hg and the high mean cardiac weight of the animals of this group clearly indicated that at one period or another during the last five weeks hypertension had probably also occurred in the other animals.

The mean *adrenal* and *pituitary* weight was significantly depressed by desoxycorticosterone in Groups 2 and 4 in comparison with the corresponding controls (Groups 1 and 3). This indicates that the well-known "compensatory atrophy" effect produced by desoxycorticosterone acetate, which consists in diminishing adrenal cortical development due to inhibition of production of pituitary corticotrophin, is independent of the dietary intake of sodium chloride.

The *thymus* weight is rather variable in all groups and a significant thymus atrophy was observed only in the animals receiving desoxycorticosterone acetate

plus sodium chloride. It is dubious, however, whether this should be considered as showing that the antithymus effect of desoxycorticosterone acetate is conditioned by dietary sodium chloride since atrophy of the thymus is a consequence of any type of stress and the animals in this group were obviously most severely damaged.

The *plasma sodium* concentration was determined by the micro modification of the method of McCance and Shipp[7] and is expressed in the last column of Table II in milliequivalents per liter of plasma. It will be noted that an extraordinarily high plasma sodium value was obtained in animals receiving desoxycorticosterone acetate plus sodium chloride (Group 4). In comparison with the corresponding control groups treated with desoxycorticosterone acetate but kept on the diets free of sodium chloride (Group 2), the increase is highly significant ($P<0.01$). It is also noteworthy that the mean plasma sodium concentration in Group 1 is significantly lower (P between 0.03 and 0.02) than in the corresponding controls receiving no desoxycorticosterone acetate treatment but kept on a sodium chloride-containing diet (Group 3). As indicated in our earlier publications, an increased sodium/chloride ratio is rather characteristic of animals overdosed with desoxycorticosterone while receiving diets which contain normal or high amounts of sodium. However, this is generally the result of a marked decrease in plasma chlorides and is only accompanied by a slight increase in plasma sodium. The unusually marked hypernatremia observed in Group 4 of the present experiment may be due to the preliminary sodium depletion of these animals during the first four weeks of the experiment.

Previous observations had shown that severe renal hypertension (produced with the "endocrine kidney" technique) causes the same cardiovascular changes as overdosage with desoxycorticosterone acetate, but there this effect was independent of the sodium intake.[5] It is probable, therefore, that the failure of desoxycorticosterone acetate to cause lesions in the cardiovascular system, in the absence of sodium, is due to its inability to increase the production of renal pressor hormone unless sufficient sodium is available.

These observations are in agreement with that interpretation of the pathogenetic mechanism governing the production of "fibrinoid diathesis," according to which desoxycorticosterone acetate acts through the intermediation of the kidney. Presumably this substance increases the production of renal pressor hormones, as a result of the transformation of certain nephrons into "endocrine nephrons," but this occurs only in the presence of sodium. On the other hand, excessive production of renal pressor hormone damages the cardiovascular system irrespective of the sodium intake.

SUMMARY AND CONCLUSIONS

Rats maintained on a sodium-free and chloride-free synthetic diet tolerated otherwise fatal doses of desoxycorticosterone acetate.

Sodium chloride deficiency was also most effective in preventing the renal and cardiac enlargement, nephrosclerosis, myocarditis, hypertension, and periarteritis nodosa normally caused by excessive amounts of desoxycorticosterone

acetate; however, it did not prevent the atrophy of the adrenal cortex and pituitary, which results from overdosage with this corticoid.

From this, in conjunction with our previously published observations, it is concluded that sodium is essential for the renal, and, through the intermediation of the kidney, for the cardiovascular actions of desoxycorticosterone acetate.

ACKNOWLEDGMENT

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NORMAL AND IMPAIRED FUNCTION OF THE LEG VEINS

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SUPERFICIAL varicosities and old, healed thrombophlebitis of the leg veins are often associated with secondary changes of the skin and subcutaneous tissue, particularly edema, pigmentation, and ulceration. Venous mechanics in the normal leg are fairly well understood, but the circulatory effects of chronic disorders of the leg veins and the etiology of the secondary changes are somewhat obscure. It is the purpose of the present report to describe the results of comparative studies of venous mechanics in the legs of normal subjects and of patients with disorders of the leg veins which have led to the development of edema, pigmentation, and ulceration. On the basis of these studies, suggestions are made as to the means by which secondary changes in skin and subcutaneous tissue may result from disorders of the leg veins.

The normal mechanics of venous return from the legs are indicated by the arrangement of valves in the leg veins. Both superficial and deep veins are valved to permit blood to flow only toward the heart. The perforating veins, which connect the two systems, permit flow from superficial to deep veins, but not in the reverse direction, except below the ankle. McPheeters[1] has pointed out that the muscles of the leg, by compressing the deep veins during contraction, drive the blood toward the heart, flow in the reverse direction being prevented by the valves. In a patient with superficial varicosities, he demonstrated by the use of radiopaque material that blood in the superficial system entered the deep channels and was carried up the leg when the muscles were alternately contracted and relaxed by a stepping exercise. He also demonstrated that when downward flow through the varicosities was checked by a tourniquet around the thigh, the pressure within the varicosities below the tourniquet was considerably lowered by exercise, indicating that blood was being drawn from the varicosities through the perforators into the deep system. In normal subjects, blood from the superficial veins passes very freely through the perforators and into the deep system, as has been demonstrated radiographically by Bauer[2] and by others after him. By an indirect method of measuring pressure in the lower end of the saphenous vein, Beecher and associates[3] found that venous pressure at the ankle of an erect subject attained its full hydrostatic head (up to heart level) only on prolonged

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quiet standing. During walking, the pressure fell to much lower levels, rising when weight was borne on the foot, and falling when the foot was lifted. The mean pressure during walking was reduced to less than half the level during quiet standing. It was concluded by Beecher that blood in the superficial veins is carried off to a considerable extent through the deep system during exercise in the upright position. Similar observations on venous pressure at the ankle of normal persons have been reported recently by Henry[4] and by Pollack and Wood,[5] both using direct pressure methods. Henry found that the pressure fall on walking was less when the leg was heated than when it was cool, and suggested that this resulted from the increased rate of blood flow into the heated leg.

Much less information is available about venous mechanics in subjects with disorders of the leg veins. In patients with varicosities, Beecher[6] found that the pressure in superficial veins at the ankle stood at the full hydrostatic head in the erect subject and was relatively unaffected by exercise. Veal and Hussey[7] measured popliteal vein pressures in the standing subject and reported that mean pressures were stable during exercise in normal persons but became elevated in cases of femoroiliac thrombosis. Comparison of oxygen saturation in varicose and in normal superficial veins was made by Holling, Beecher, and Linton,[8] since it was thought that degenerative skin changes in the former subjects might result from a diminution in the rate of blood flow. No significant differences were found, however.

METHODS

Direct venous pressures were recorded by means of a Hamilton manometer. The lower end of the saphenous vein or a vein on the dorsum of the foot was well threaded with a No. 19 needle after preliminary procaine infiltration. The needle was filled with heparin and closed by an attached three-way stopcock. A needle so prepared and well-supported by adhesive tape will remain in position, and patent, for a long time, allowing repeated pressure determinations and withdrawal of blood samples. If the needle is well placed, it does not interfere with walking. No evidence of venospasm was encountered. For pressure determinations, the needle was connected with the lead tubing of the manometer by a length of No. 8 ureteral catheter. Mean pressures were determined by planimetric integration of the record.

Blood oxygen determinations were carried out in duplicate by the method of Van Slyke and Neill, and were required to check within 0.1 volume per cent.

For venography, 35 per cent Diodrast was injected slowly through the catheter attached to the needle in quantities up to a total of 80 cubic centimeters. Stereoroentgenographs were found necessary in order to differentiate between deep and superficial veins.

All studies were conducted with the patient in a standing position or on a tilt table at an angle of 70 degrees. Two standard exercises were used. "Rocking" consisted of rising on the toes so that the heels were one to two inches above the floor, and then settling back to bear most of the weight on the heel. This was repeated at a rate of about one cycle in two seconds. Standing-walking was performed at the same rate, each foot being lifted several inches off the

floor. Studies were conducted in an air-conditioned room at a temperature of 23 to 25° centigrade.

RESULTS

Normal Subjects.—Observations have been made on eleven normal subjects. The results obtained with the rocking exercise are summarized in Table I. On motionless standing, the venous pressure at foot or ankle becomes equivalent to that of a column of water extending from the ankle approximately to the level of the right atrium. As indicated in Fig. 1,*a*, rocking produces large pressure fluctuations, the maximum occurring during contraction of the calf muscles and the minimum during relaxation. As exercise proceeds, the mean pressure rapidly declines to a level which is fairly stable so long as the exercise is kept constant. When the subject stops rocking and leans against a support, the pressure at once assumes its minimum value and then slowly rises in nearly a straight line. If pressures are expressed in terms of change from the full hydrostatic head (designated as a pressure of "O"), the mean pressure during rocking averaged -32 ± 7.0 mm. Hg; the average pressure following exercise was -51 ± 7.0 mm. Hg; and the rate at which pressure rose to the resting level was 2.0 ± 0.8 mm. Hg per second, taking on the average twenty-five seconds to return to its full value. The mean pressure during standing-walking or walking on a treadmill is often lower than during the rocking exercise (Fig. 2,*a*), but performance of the latter is more easily standardized, and it has been used as the basic comparative test throughout the study.

Both mean pressure during exercise and the rate of pressure return on subsequent rest may be affected by circumstances which alter the rate of blood flow into the leg. Figs. 1 and 2 illustrate the effect of a warm environment in decreasing the fall of mean pressure during both types of exercise and in increasing the rate of pressure return at rest. A similar result was obtained in a normal subject after he had walked on a treadmill at 3 miles per hour for six minutes. Immediately prior to this, a pressure drop of -50 mm. Hg produced by rocking had returned during rest to the full hydrostatic head at a rate of 2.3 mm. Hg per second. When treadmill-walking was abruptly stopped after six minutes and the subject stood quietly, the pressure rose from -35 mm. Hg at a rate of 9.0 mm. Hg per second.

Diodrast injected into the superficial veins of the foot or ankle passes into both superficial and deep systems of the leg. The passage into the deep system takes place during motionless standing, as well as when rocking is carried out by the subject during injection. The location of valves is indicated by a localized oval enlargement of the vein. Valves occur more frequently in the deep veins than in the superficial. That portion of the deep system which is filled by Diodrast has a much greater capacity than the portion of the superficial system which is so demonstrated. When Diodrast is injected while the subject is rocking, pathways from the superficial to the deep system are sometimes brought out which were not filled during motionless standing. The reverse has not been observed. Films taken while the subject is bearing his weight on the toes show a lateral shift in position and distortion of the shape of some of the deep channels, but very little change in the superficial veins.

TABLE I. NORMAL SUBJECTS

SUBJECT	RESTING PRESSURE*	MAXIMUM PRESSURE DURING EXERCISE	MEAN PRESSURE DURING EXERCISE	MINIMUM PRESSURE AFTER EXERCISE	RATE OF RETURN (MM.HG/SEC.)	BLOOD O_2 (VOL. %) REST	PER CENT SATURATION	BLOOD O_2 (VOL. %) EXERCISE	PER CENT SATURATION
R. M.	0	0	−28	−62	2.4	12.8	68	11.2	59
G. R.	−2	+13	−26	−43	1.0				
I. S.	+2	− 7	−31	−58	1.3				
H. O.	−7	−14	−35	−54	1.3	10.0	53	11.3	60
M. A.	0	0	−28	−47	1.3	16.8	76	16.1	73
B. E.	0	0	−31	−44	2.6	13.0	60	13.0	60
W. A.	0	0	−29	−45	1.7	10.9	57	10.6	56
H. I.	0	0	−32	−53	3.0	11.1	58	11.1	58
P. A.	0	+ 2	−30	−59	3.1	3.4	28	3.4	28
S. I.	0	0	−50	−54	1.1	12.7	60	11.9	56
S. H.	0	+21	−35	−67	2.2	9.6	53	8.0	44
Average			−32	−52	1.9		57		55
Standard deviation			6.6	7.7	.8		13		20
Standard error			2.1	2.4	.2		5		7

*All pressures in millimeters of mercury, expressed as deviation from full hydrostatic head (needle to heart).

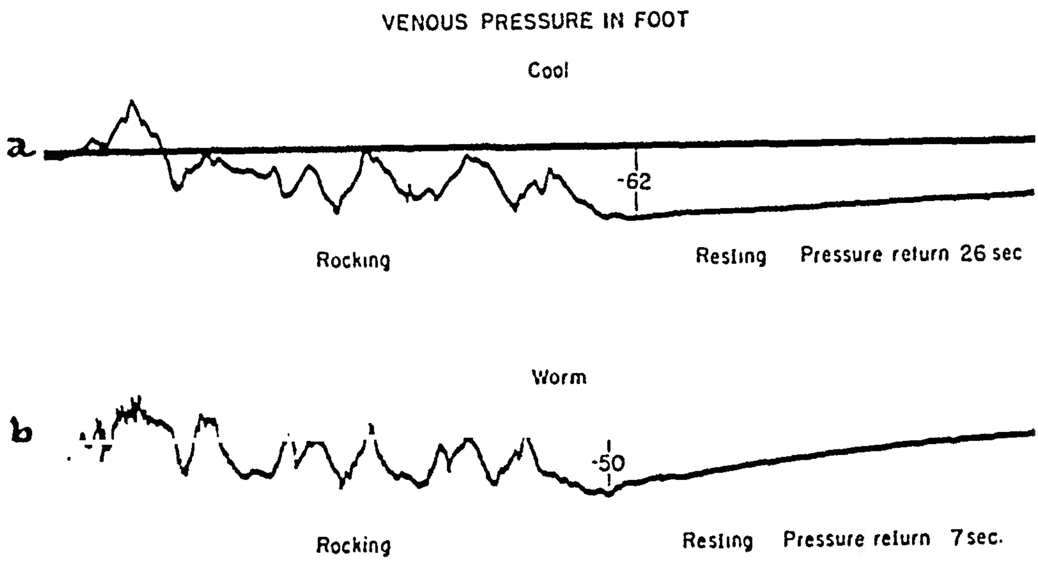

Fig. 1.—*a*, Normal subject, erect position. Effect of rocking exercise on pressure in saphenous vein at the ankle at an ambient temperature of 23 to 25° centigrade. Horizontal line indicates full hydrostatic pressure head from needle to heart. Pressures are expressed in terms of deviation from this level in millimeters of mercury.

b, Same subject. Effect of warming subject by wrapping body in a heated blanket.

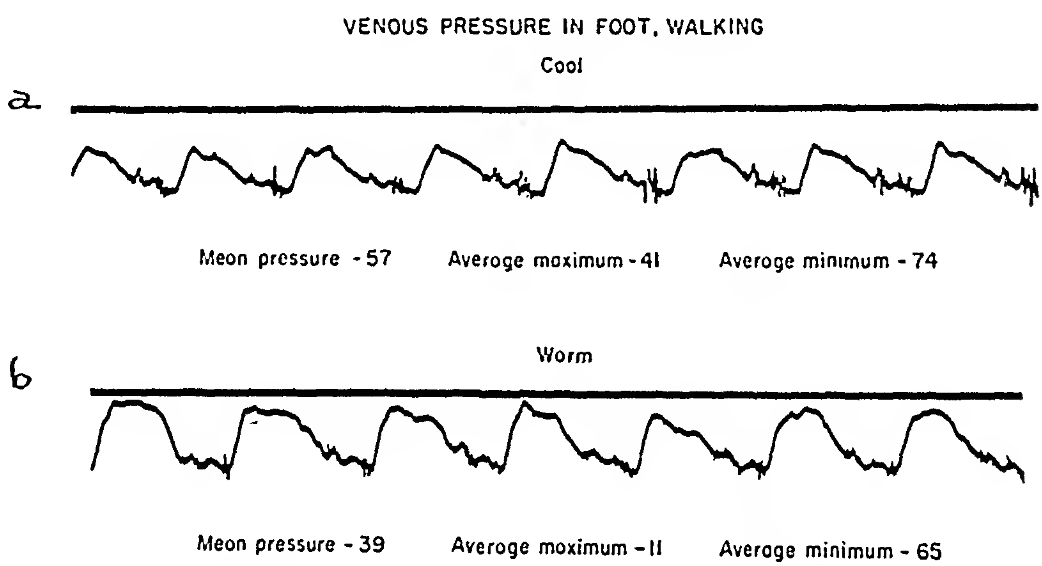

Fig. 2.—*a*, Normal subject. Effect of standing-walking on pressure in saphenous vein at the ankle at an ambient temperature of 23 to 25° centigrade. Horizontal line indicates full hydrostatic pressure head from needle to heart. Pressures are expressed in terms of deviation from this level in millimeters of mercury.

b, Same subject. Effect of warming body in a heated blanket.

The combined results of pressure measurements and venography provide a very clear demonstration of the means by which return flow from the superficial veins is managed when the subject is moving about in the upright position. As has been pointed out by McPheeters[1] and by Beecher,[3] blood is forced upward through the deep channels by the squeezing action of the calf muscles. Competent perforators prevent transmission of this pressure to the superficial system. During relaxation, the superficial veins drain through the perforators into the deep system. The hydrostatic column of the superficial system is broken by drainage of intervalvular segments of the superficial veins, with a consequent fall in pressure. Superficial pressures can be reduced markedly even by infrequent muscular contractions, because the capacity of the deep system is much larger than that of the superficial. By these means the superficial tissues of the leg are normally drained at a surprisingly low pressure when the subject is in the upright position.

The valvular and muscular arrangements by which the superficial veins of the leg are drained seem not to be duplicated in the venous system of the arm. Pressures in the vein on the radial border of the forearm near the wrist have been measured in three normal subjects. When the arm is allowed to hang by the side, a pressure is developed which is 2.0 to 4.0 mm. Hg in excess of the hydrostatic head as measured from the fourth sternocostal junction. Competency of the valvular system is demonstrated by elevating the arm to drain the veins and then lowering it quickly. The pressure is then 20 to 30 mm. Hg below the previous level, but begins to return at once in nearly a straight line, regaining its former value in five to ten seconds. Clenching the fist of the dependent arm causes a momentary elevation of pressure up to 40 or 50 mm. Hg above the resting level, depending upon the violence of contraction. During relaxation, however, the pressure does not fall more than 4.0 to 5.0 mm. Hg below the resting level. The superficial veins of the dependent forearm are apparently not emptied in segments by drainage into the deep system during muscular contraction as is the case in the leg. In two subjects Diodrast was introduced into the radial vein during alternate clenching and opening of the fist. In one case the dye remained in the superficial system of the forearm; in the other, it also entered veins in the interosseous region. In both cases, all channels joined the basilic vein above the elbow.

The oxygen content of blood from the superficial veins of the leg was determined in nine subjects (Table I). When they were standing quietly at room temperature, the average percentage of saturation was 57 ± 13. Rocking produced no significant change. In Subject R. M., change from room temperature to a hot environment resulted in a rise of percentage saturation from 68 to 94, suggesting that most of the blood was passing through arteriovenous communications. Subsequent walking on a treadmill for five minutes reduced the value to 30 per cent. The low value during active exercise indicates a large share of muscle blood. Since perforating veins in the foot are valved for outward flow and those in the calf for inward flow, it is presumed that this muscle blood in the lower end of the saphenous vein originates from foot muscles. The apparent contribution of arteriovenous shunts and muscle flow from the foot to the

composition of blood in the lower end of the saphenous vein greatly restricts the validity of this measurement as an index of circulation in the adjacent skin.

Patients With Venous Disorders of the Leg.—Eight patients were studied who had disorders of the venous system of the leg. The data collected on these patients, together with a descriptive note as to their condition, are presented in Table II. All patients had slight to moderate ankle edema, and all had ulcers or a history of ulceration on the leg studied, except for Patients H. E. and G. O., who had brown pigmentation over the medial surface of the lower third of the leg.

The resting venous pressure of these patients was at or slightly above the "O" level (fourth costochondral junction), with the exception of Patient T. H., who had marked elevation associated with a large femoral arteriovenous fistula. On rocking, the patients in this group displayed behavior in striking deviation from the normal. The mean pressure during exercise was not reduced or was reduced much less than normal. On subsequent quiet standing the pressure returned to its full value at a much more rapid rate than in normal subjects. For the group, the mean pressure during exercise was -1 ± 13 mm. Hg, and the pressure immediately after exercise was -22 ± 21 mm. of mercury. In three subjects the pressure was not reduced in the postexercise period, but immediately regained the resting value. In the remainder, the rate of pressure return during rest was 7 ± 2 mm. Hg per second. One further difference between this group and the normal subjects was noted, namely, the maximum pressures which occurred during exercise. At the onset of rocking, even normal subjects will show an initial high peak of pressure (from 15 to 78 mm. Hg, in the present study). Within three cycles the peak at each elevation of the heel is more or less constant and rarely rises more than a few millimeters of mercury above the zero level (Table I). In the abnormal group, even after exercise has become well established, pressures at each cycle continue to rise well above the zero level (Table II). These high pressures are probably effective in further dilating superficial veins and in breaking down their valves. The most favorable response to exercise in the group was exhibited by Patient M. D., who had an old thrombophlebitis and a chronic ankle ulcer. The average of several trials by this patient yielded a mean reduction during exercise of -16 mm. Hg, a minimum of -49 mm. Hg, and a return rate of 7.6 mm. Hg per minute.

In general, the patients of this group failed to exhibit a normal reduction of mean pressure in the superficial system during exercise, sustained repeated high peaks of pressure in the superficial veins during exercise, and had a rapid return to full pressure at rest. Typical pressure tracings made during exercise are shown in Fig. 3.

The means by which these deviations from normal function are produced depend upon the particular venous disorder. When deep veins of the calf have been occluded by thrombophlebitis, such channels as are recanalized appear to have lost efficient valvular function and can no longer provide a low pressure region to accept blood rapidly from the superficial veins. The functional result, so far as the superficial system is concerned, is quite similar to that which exists normally in the forearm, except that the pressures involved are much higher.

TABLE II. VENOUS DISORDERS

SUBJECT	REMARKS	RESTING PRESSURE*	MAXIMUM PRESSURE DURING EXERCISE	MEAN PRESSURE DURING EXERCISE	MINIMUM PRESSURE AFTER EXERCISE	RATE OF RETURN (MM. HG/SEC.)	BLOOD O_2 (VOL. %) REST	PER CENT SATURATION	BLOOD O_2 (VOL. %) EXERCISE	PER CENT SATURATION
M. K.	Old thrombophlebitis	0	+35	0	0	†				
D. A.	Varix	0	+68	+ 7	−47	4.7	9.0	50	7.9	44
T. H.	Varix with femoral A-V fistula	+23	+62	+23	−47	4.0	7.2	47	7.6	50
S. O.	Varix	0	+57	−10	−36	8.0	7.7	41	8.8	47
M. D.	Old thrombophlebitis	+ 6	+28	−16	−49	7.6	8.4	51	8.2	49
H. E.	Old thrombophlebitis	+ 8	+40	+ 5	0	†	9.5	49	9.8	51
G. O.	Varix	+ 2	+24	0	−17	8.5	8.9	46		
G. A.	Old thrombophlebitis	0	+85	−16	0	†	6.3	30	6.2	29
Average				− 1	−22	6.6		45		45
Standard deviation				13	21	4.5		8		
Standard error				6	7	2.0		3		

*All pressures in millimeters of mercury, expressed as deviation from full hydrostatic head (needle to heart).
†Immediate.

Venograms of such a subject (G. A.), with old thrombophlebitis but no evident superficial varicosities, showed faint, irregular filling of a deep channel, with no apparent valves, and a dense shell of dilated, tortuous veins up to the diameter of a lead pencil surrounding the leg in the edematous subcutaneous tissue. In this case, the visible capacity of the superficial system was much greater than the deep. Under these circumstances, whatever valvular function may remain in the deep system is relatively ineffective in emptying the superficial veins. Here, the dilatation of superficial veins is apparently secondary to loss of function in the deep system.

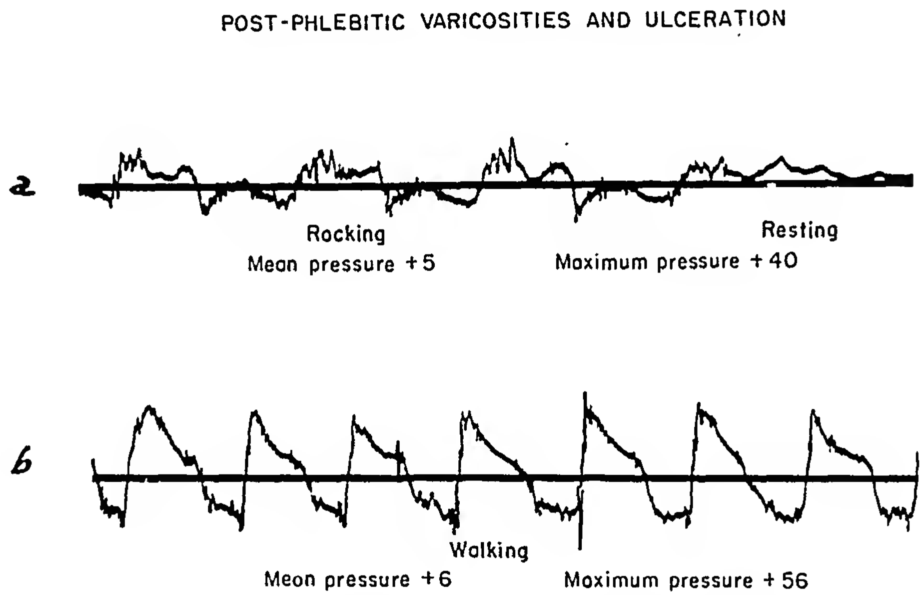

Fig. 3.—*a*, Patient with postphlebitic varicosities and ulceration. Effect of rocking exercise on venous pressure at the ankle. Pressures expressed as in previous figures.

b, Same patient. Effect of standing-walking.

Where dilatation and loss of valves in the superficial system is primary, as in most cases of varicosity, persistent pressure elevation is on a different basis. Here, the hydrostatic column cannot be broken by drainage into the deep system, even though the latter is functioning well, because of the loss of superficial valves. As demonstrated by McPheeters[1] and by Mahorner and Ochsner,[9] the application of a tourniquet at a carefully adjusted pressure above the knee will cause varicosities below the tourniquet to empty during exercise in cases where the valves of perforators and deep veins are competent. This is because these varicosities are no longer continuously supplied with blood from above. Pressure tracings made with and without such a tourniquet are shown in Fig. 4. This patient had large varices but competent perforators, as demonstrated by the Trendelenburg test. On venography, a large, deep vertical vein which emptied well and had competent valves could be seen in the leg. As in the previous case, the dye was distributed by exercise through a dense shell of varicosities under the skin of the calf.

The oxygen content and percentage saturation of blood from the superficial veins of this group were determined (Table II). The average percentage saturation was 45 per cent. This does not represent a significant variation from the normal.

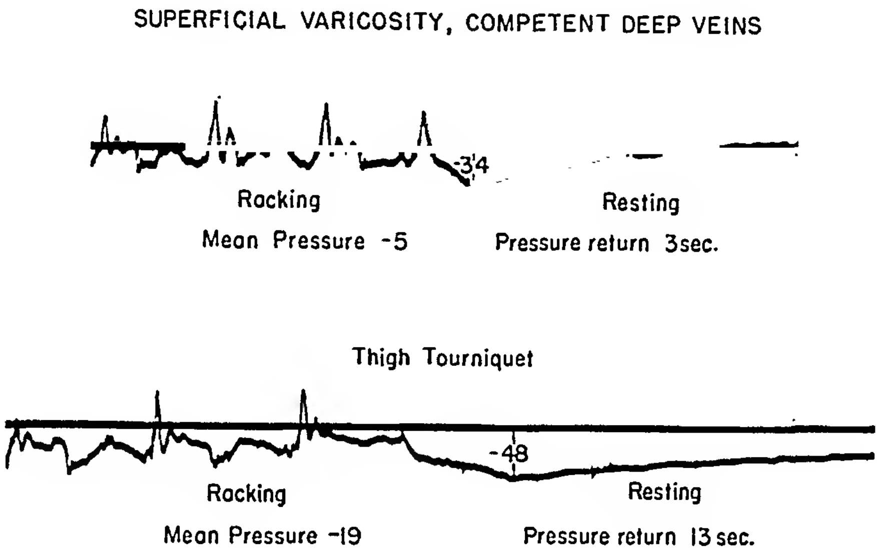

Fig. 4.—Patient with varicosities but competent perforators and deep veins. Upper figure shows the effect of the rocking exercise on venous pressure at the ankle. Lower figure shows the change resulting from application of a tourniquet to the thigh.

DISCUSSION

The fundamental abnormality which has been demonstrated in subjects with chronic venous disorders and secondary skin changes is loss of the ability to drain the skin and subcutaneous tissue of the leg at a low pressure when the subject is erect. There appears to be a variety of means by which this primary abnormality may produce secondary changes in the affected leg.

Most writers have agreed that the edema associated with varicose veins and thrombophlebitis is, at least in part, the result of increased venous pressure. Our quantitative studies confirm this view.

Skin pigmentation and the development of ulcers are usually ascribed to nutritional disturbances of the skin. The word "stasis" is often used to denote the mechanism of this disturbance, implying a decreased blood flow to the skin of the affected region. The primary agency of a decreased blood flow to the skin appears, however, to be doubtful. It is true that the normal leg is admirably equipped to benefit, in terms of blood flow, from the erect position. Because the hydrostatic head of the venous column is frequently and effectively broken by muscular contraction, while the same is not true of the arterial column, the resultant head of pressure by which blood is driven through the vessels of the leg is normally much greater, during motion, in the erect than in the recumbent position. This benefit is not available to a leg which has lost the normal valvular function of its veins. There is, however, no apparent reason to assume that the

rate of blood flow through such a leg is significantly decreased in the upright position below that in the recumbent position, since the hydrostatic pressures of arterial and venous systems are balanced. On the face of it, bed rest, which favors the healing of ulcers associated with venous disorders, should make no particular difference to the total volume rate (volume per unit time) of blood flow through the skin. The velocity (distance per unit time) of blood flow through dilated superficial veins will, of course, be slow even though the volume flow is normal, because of the large cross-sectional area. It is, however, the capillary circulation which is important to skin nutrition. If the capillaries of the skin are also dilated, the velocity of flow through them will likewise be decreased, and skin nutrition might well be impaired even with a normal volume flow. There appears to be no adequate information as yet on this point.

It seems quite possible that chronic edema, resulting from prolonged elevation of the venous pressure, may be the important factor in initiating degenerative skin changes. There are at least two means by which chronic edema might adversely affect the skin. The simplest is by mechanical disruption of cutaneous and subcutaneous structures. The second, and possibly the more important, is the interference with tissue nutrition which must result from the physical isolation of cells from their capillary supply by a sheath of edema fluid. Transfer of material between cell and capillary at the normal rate will then require a greater than normal diffusion gradient, a handicap which must reflect adversely upon the metabolic processes of the cell.

It is apparent that skin changes, once begun, are furthered by mechanical trauma, repeated local infection, lymphatic blockage, and fibrosis. The suggestion is made that the primary factor may well be elevation of the venous pressure, with the production of chronic edema and possibly capillary dilatation, and the consequent impairment of skin nutrition. If this suggestion is correct, the beneficial effects of recumbency and pressure bandages are easily understood.

The quantitative results of the present study have certain applications to the therapeutic use of pressure bandages. Patients with chronic venous disorders who are up and about maintain pressures in the leg veins which greatly exceed the normal, often by amounts of 50 mm. Hg or more. It is apparent that any bandage which is intended to counteract these pressures must be capable of firm resistance to increase in volume of the leg around which it is applied. A snugly fitting Unna paste boot meets this requirement well. It yields little, so that a small increase in leg volume (due to edema and venous distention) is met by a sharp rise in counterpressure. On the other hand, elastic bandages are not effective unless they are very firmly applied and so constructed that they strongly resist any further stretch. The full benefit of a pressure bandage will not be obtained unless it is applied firmly enough to prevent the formation of edema when the patient is up and about.

Where obliteration of an incompetent superficial system is the object desired, as in patients with varicosities and a competent deep system, it is apparent that surgical procedures, such as multiple ligation and injection or stripping and excision,[10] are to be preferred.

SUMMARY AND CONCLUSIONS

1. A comparative study has been made of venous function in the legs of normal subjects and of patients with chronic disorders of the leg veins and secondary skin changes.

2. The subjects with venous disorders were found to have lost the normal ability to effect venous drainage of the superficial tissues of the leg at a low pressure in the upright position.

3. It is suggested that this abnormality may be primarily responsible for the development of secondary skin changes.

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PLASMA TOCOPHEROL LEVELS IN CARDIAC PATIENTS

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THE importance of the tocopherols in maintaining normal muscle function was established following Evans'[1] description of muscular dystrophy in the offspring from rats fed a low vitamin E diet. In 1944 Houchin and Smith[2] reported myocardial damage in rabbits deprived of vitamin E. They attributed the sudden death of their animals to cardiac failure. Two other studies, by Mason and Emmel,[3] and by Martin and Faust,[4] reported myocardial lesions in rats maintained on a diet deficient in tocopherols. Changes in the electrocardiographic patterns of vitamin E-deficient cattle[5] and rabbits[4] have also been described. The possible relationship between vitamin E and cardiac function has been approached more specifically by Govier and co-workers,[6] who have studied the effect of tocopherols on cardiac muscle metabolism. Holman[7] found that the development of experimental arteritis in dogs could in some cases be prevented by vitamin E treatment. Recently Shute and his associates[8] have reported clinical improvement in patients with various cardiovascular lesions, following tocopherol therapy.

In view of these findings suggesting a relationship between tocopherol deficiency and cardiac muscle changes, an attempt has been made to determine whether patients with heart disease present any evidence of subnormal tocopherol nutrition. At present there are no known clinical evidences of tocopherol deficiency in man. The laboratory determination of plasma tocopherol level is so far the only criterion of tocopherol nutrition.

MATERIAL AND METHOD

The tocopherol content of the blood plasma was determined in twenty-one healthy young adults, sixty-two patients known to have cardiac disease, and forty-two individuals who constituted a random sample of the hospital ward population. The total tocopherols were determined by the chemical method of Quaife and co-workers,[9,10] and the results were expressed as milligrams of α tocopherol per 100 ml. of plasma.

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RESULTS

I. *Plasma Tocopherol Levels in Normal Subjects.*—The available data concerning plasma tocopherol levels in normal subjects are summarized in Table I. As indicated here, various groups have reported essentially similar values for

TABLE I. NORMAL PLASMA TOCOPHEROL LEVELS

	NUMBER OF CASES	MEAN (MG. PER CENT)	S. D.
Wechsler, Mayer, and Sobotka	12	0.96	
Quaife and Harris	13	1.20	±0.22
Darby, Cherrington, and Ruffin	10	1.06	±0.06
Harris, Hickman, Jensen, and Spies	70	1.04	±0.32
Present report	21	1.09	±0.17

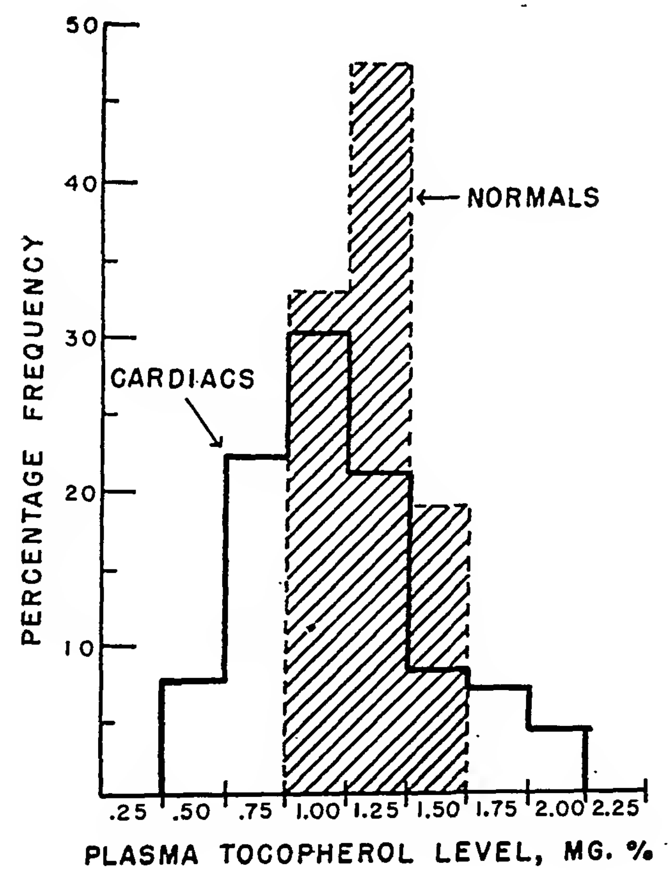

Fig. 1.—Frequency distribution of plasma tocopherol levels in normal subjects and in cardiac patients.

plasma tocopherol levels in normal individuals. In the present investigation the average tocopherol level in twenty-one normal adults was 1.09 ± 0.17 mg. per cent, a value which agrees with those reported from other laboratories.

II. *Plasma Tocopherol Levels in Cardiac Patients.*—Plasma tocopherol levels were determined in sixty-two patients with various types of heart disease. They were equally distributed as to age and sex. The average value was 0.94 ± 0.35 mg. per cent, ranging from 0.25 to 1.89 mg. per cent. Fig. 1 shows the distribution of plasma tocopherol levels in normal and cardiac patients. The mean tocopherol level of cardiac patients was significantly lower than that of young healthy adults, and there was a greater incidence of low tocopherol levels in cardiac patients than in normal individuals.

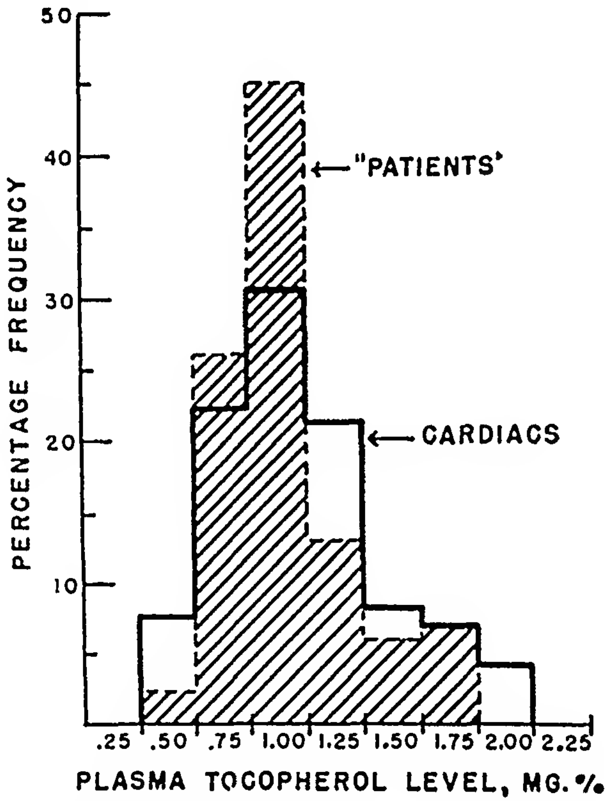

Fig. 2.—Frequency distribution of plasma tocopherol levels in the general patient group and in cardiac patients.

III. *Plasma Tocopherol Levels in a General Patient Group.*—The next problem was to determine whether the pattern of tocopherol levels in patients with heart disease was different from that in other hospital patients. A third series of individuals was chosen at random from the hospital population. No effort was made to select the patients according to type of disease, but the group was equally distributed with regard to age and sex. The average plasma tocopherol level for this group was 0.92 ± 0.29 mg. per cent, ranging from 0.42 to 1.68 mg. per cent. The mean tocopherol level in the general patient group was not statistically different from that found in the cardiac group, but it was again significantly lower than the mean value for young healthy adults. Fig. 2 shows the frequency distribution of tocopherol levels in the two groups, general and

cardiac patients. The pattern of tocopherol levels in patients with heart disease was no different from that of other hospital patients picked at random. Thus, although some cardiac patients show lower tocopherol levels than normal subjects, this trend is not peculiar to individuals with cardiac disease, but is apparently a characteristic of patients in general.

IV. *Relation of Tocopherol Level to Cardiac Classification.*—The cardiac patients were divided into four groups according to their ability to perform physical activity. This method of classification, established by the New York Heart Association,[14] defines the four classes of cardiac patients as follows:

Class I: Patients with no limitation of ordinary physical activity.
Class II: Patients with slight limitation of ordinary physical activity.
Class III: Patients with marked limitation of physical activity.
Class IV: Patients who are unable to carry on any physical activity.

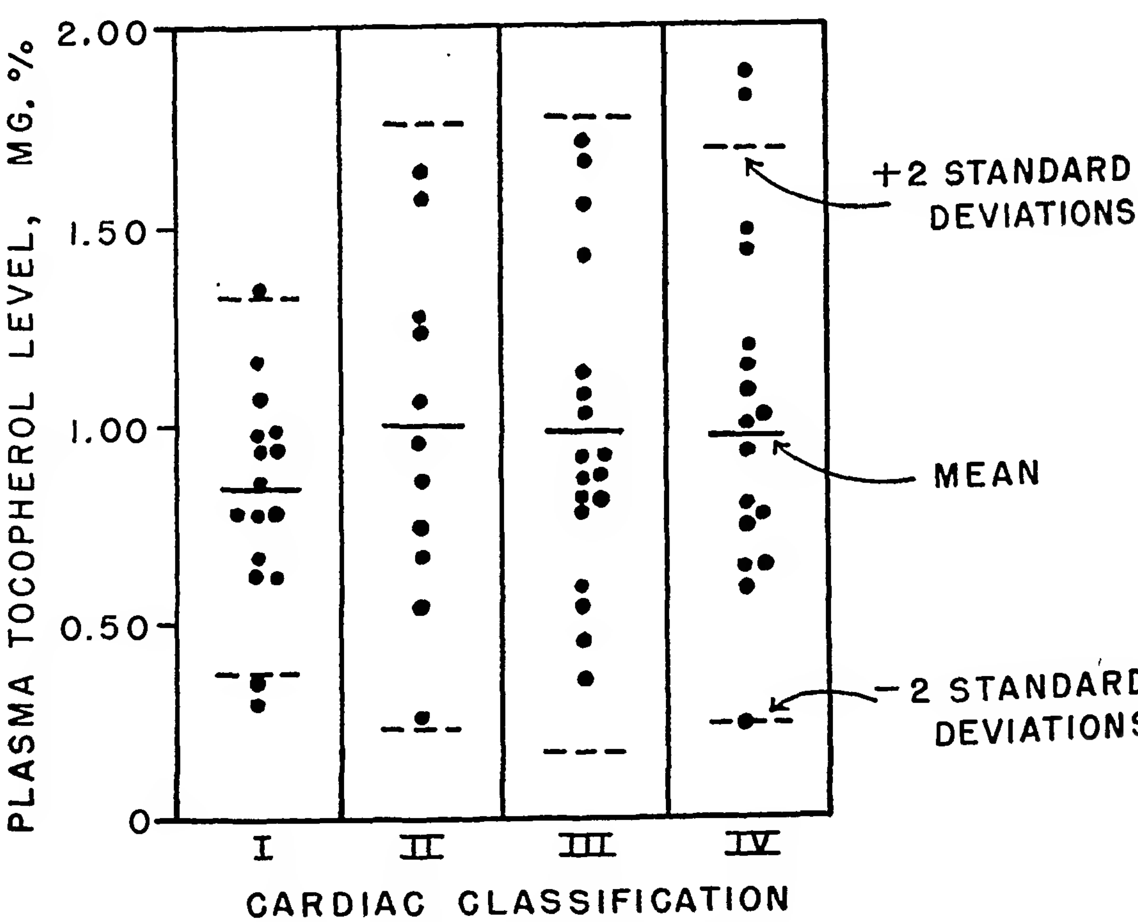

Fig. 3.—Relation between cardiac classification and plasma tocopherol level.

The plasma tocopherol levels of patients in each of the four cardiac classes were then compared. In Fig. 3 the individual plasma levels have been plotted against cardiac classification. The mean plasma tocopherol was not significantly different in any of these classes. Furthermore, the incidence of low tocopherol levels was no greater in those patients showing more severe cardiac im-

pairment. If plasma tocopherol levels are a measure of tocopherol nutrition, then these data give no evidence for a direct relationship between tocopherol nutrition and cardiac muscle function.

V. *Relation of Tocopherol Level to Sex, Color, and Age.*—Since the pattern of tocopherol levels was essentially similar in cardiac patients and patients in general, data from the two groups were combined for further study. In this group of 104 patients, no correlation was found between tocopherol level and sex or color. However, there is evidence of a significant positive correlation between plasma tocopherol and age. This relationship is shown when the individual plasma tocopherol levels are plotted against the age of the patient (Fig. 4). The degree of association between tocopherol level and age was measured statistically, and a positive correlation coefficient of + 0.343, with a standard error of ± 0.098 was obtained.

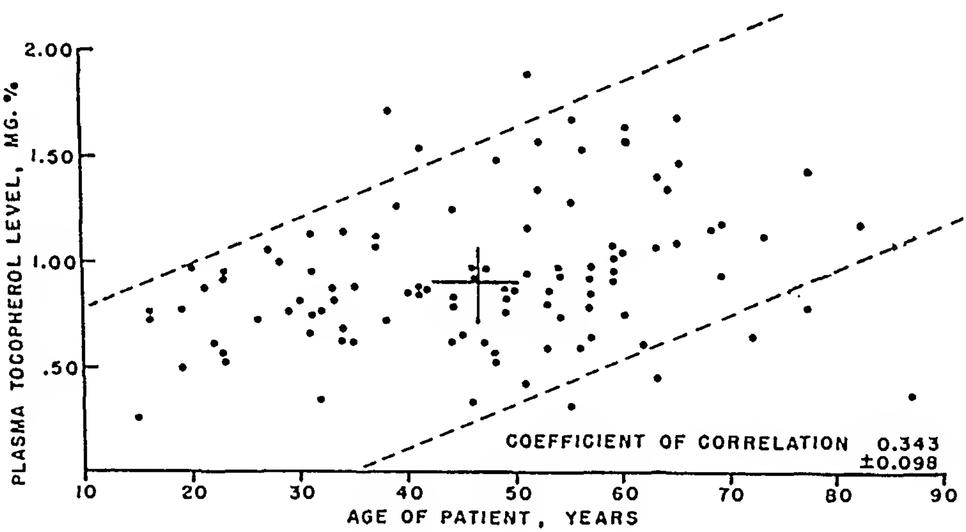

Fig. 4.—Relation between plasma tocopherol level and age.

SUMMARY

1. The average plasma tocopherol level in sixty-two patients with heart disease was 0.94 mg. per cent, a value which was significantly lower than the mean of 1.09 mg. per cent found in twenty-one healthy young adults. In addition, there was a greater incidence of very low levels among the cardiac patients.

2. The plasma tocopherol level was determined in forty-two patients constituting a random sample of the hospital population, and an average value of 0.92 mg. per cent was obtained. This value was also significantly lower than that in normal subjects, but was essentially the same as that found among cardiac patients. Furthermore, the incidence of low tocopherol levels was no greater in patients with heart disease than in hospital patients in general. In so far as plasma tocopherol levels are a measure of tocopherol nutrition, no evi-

dence was found for differences between tocopherol nutrition in cardiac patients and that in other patients picked at random from the general hospital population.

3. Tocopherol levels of patients in each of the four cardiac classes were essentially similar. No relationship was found between the tocopherol level and the severity of cardiac impairment.

4. No correlation was found between the tocopherol level and sex or color, but there was a positive correlation between the tocopherol level and age.

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THE POTENTIAL DIFFERENCES BETWEEN MULTIPLE CENTRAL TERMINALS EACH CONNECTED TO A SEPARATE SET OF LIMB ELECTRODES

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In a recent publication Groedel[1] reports that he has found significantly large potential differences between three central terminals each connected to a separate set of three limb electrodes. He does not mention the size of the resistances between the limb electrodes and the central terminals. One central terminal was attached to electrodes near the junctions of the extremities with the trunk, one to electrodes near their distal ends, and the third to electrodes near the second joints. The largest potential difference observed amounted to approximately 0.5 millivolt. It was stated that "a final electrophysical explanation" could not be given. The conclusions, however, were "that at the central terminal there is a considerable potential, which is neither zero nor approximately zero," and "that the central terminal offers no practical advantage for its further use in obtaining so-called unipolar chest leads."

It is not our purpose here to attempt either to prove or to disprove that the potential variations of a central terminal connected to the limb electrodes through large resistances are negligible, but rather to explore the situation which exists when several central terminals are joined to electrodes on the limbs in the manner specified.

METHODS

Two metal electrodes approximately 1.0 cm. in diameter were placed in the midsternal line and connected to the output terminals of a beat-frequency oscillator. In this way a low-frequency (25 cycles per second) alternating current of 0.35 to 0.5 milliampere was introduced into the chest of a normal subject. The strength of the electrical field thus set up in the body could be varied either by changing the size of the current or by changing the distance between the input electrodes. Our purpose in creating an artificial electrical field, instead of studying that associated with the heart beat, was to place the intensity of the field under our control and to substitute a simple wave form for the complicated electrocardiographic deflections.

Five German silver electrodes of the pattern commonly used in electrocardiographic studies were placed on each of the three extremities from which the

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standard limb leads are taken. The arrangement of these electrodes is shown in the diagram reproduced in Fig. 1. The electrodes labeled *1*, *2*, and *3* were approximately two inches apart and those labeled *A* and *B*, approximately five inches apart. Two additional electrodes, not shown in Fig. 1, were placed at the humeral attachments of the deltoid muscles for the purpose of taking standard Lead I. This lead was taken simultaneously with each of the other leads employed. All records were taken with the Sanborn Tri-beam electrocardiograph. Each

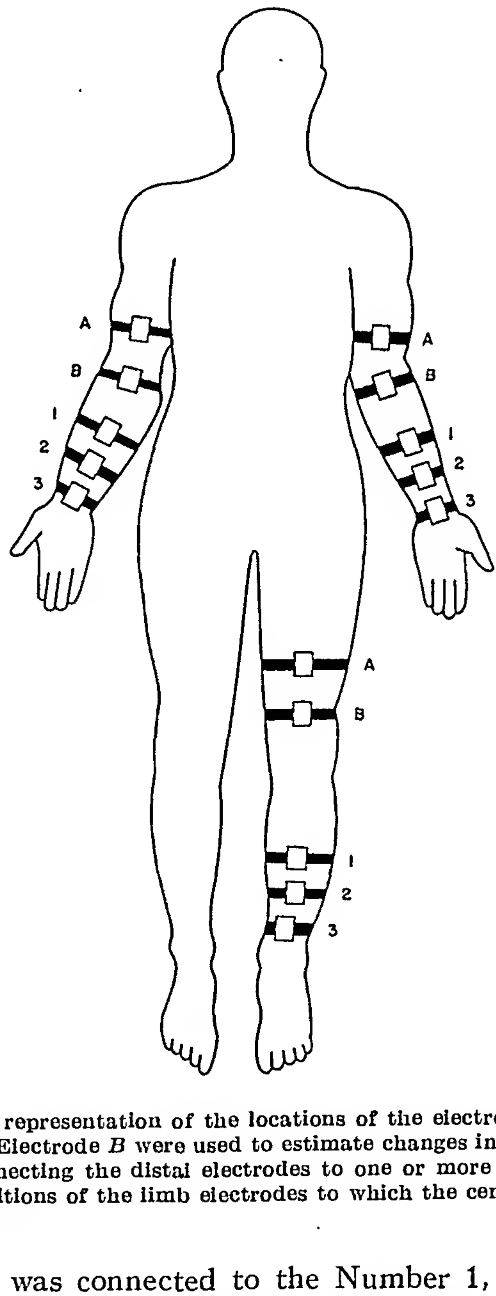

Fig. 1.—Diagrammatic representation of the locations of the electrodes in Experiments 1 and 2. Leads from Electrode *A* to Electrode *B* were used to estimate changes in the current flowing along the extremity produced by connecting the distal electrodes to one or more central terminals. Numbers *1*, *2*, and *3* indicate the positions of the limb electrodes to which the central terminals were attached.

central terminal used was connected to the Number 1, the Number 2, or the Number 3 electrodes. The more proximal electrodes, *A* and *B*, were used to obtain information concerning the flow of current along each extremity when one or more of the distal electrodes was connected to a central terminal. In Figs. 2 and 3 the *A* to *B* lead from the right arm is labeled *R*; that from the

left arm, *L*; and that from the left leg, *F*. When more than one central terminal was connected, the potentials of the various central terminals were compared by leading from one to the other.

DESCRIPTION OF EXPERIMENTS

Experiment 1.—In this instance the current and the distance between the input electrodes were adjusted in such a way as to yield deflections in Leads II and III of the maximum size that could be conveniently recorded simultaneously with Lead I on bromide paper 6.0 cm. in width. The electrocardiograph was operated at its normal sensitivity. The input current was 0.35 milliampere and it was maintained at this value with the aid of a milliammeter. All deflections were measured to the nearest 0.5 millimeter. Leads from the *A* to the *B* electrode on each extremity were taken before and after a central terminal was connected directly, that is, without resistances, to one of the sets of distal electrodes, and after first one, then a second, and then a third central terminal was connected through 5,000 ohm resistors in successive steps. Finally, the potential differences between the central terminals connected through resistors were recorded; that is, the single potential difference when only two were connected, and the three potential differences between the different pairs when three were connected.

Strips of the tracings obtained are reproduced in Fig. 2. These were cut in such a way as to avoid sections where the sine waves were distorted by the subject's electrocardiogram. The standard limb leads show very large deflections in Leads II and III and these are out of phase with the small oscillations in Lead I. Consequently, the algebraic sum of the deflections in Leads I and III is 43 millimeters. The deflections in Lead II measure 40 millimeters. Before any of the distal electrodes (*1*, *2*, and *3*) were connected through a central terminal the oscillations in the leads from the *A* to the *B* electrode on each of the three extremities (labeled *R*, *L*, and *F*) were so small as to be barely visible. At this time, therefore, the currents flowing through the internal tissues of the extremities toward or away from the trunk were of negligible magnitude. When a central terminal was joined to a set of distal electrodes without intervening resistances, the deflections in these same leads approached those of Lead I in size. On the other hand, they were not much larger after than before a central terminal was attached to the same set of limb electrodes through 5,000 ohm resistors.

They increased in amplitude when a second, and again when a third central terminal of the same kind was connected, but the currents flowing through the limbs were only about two-thirds as large after the connection of three central terminals through resistors as they were after the connection of one terminal without resistors. When two central terminals were connected to the extremities through resistors, the difference in potential between them was small. When three central terminals were connected through resistors, the differences in potential between the different pairs were somewhat larger and not all equal. The largest oscillations recorded by leading from one terminal to another are about 1.0 mm. in amplitude.

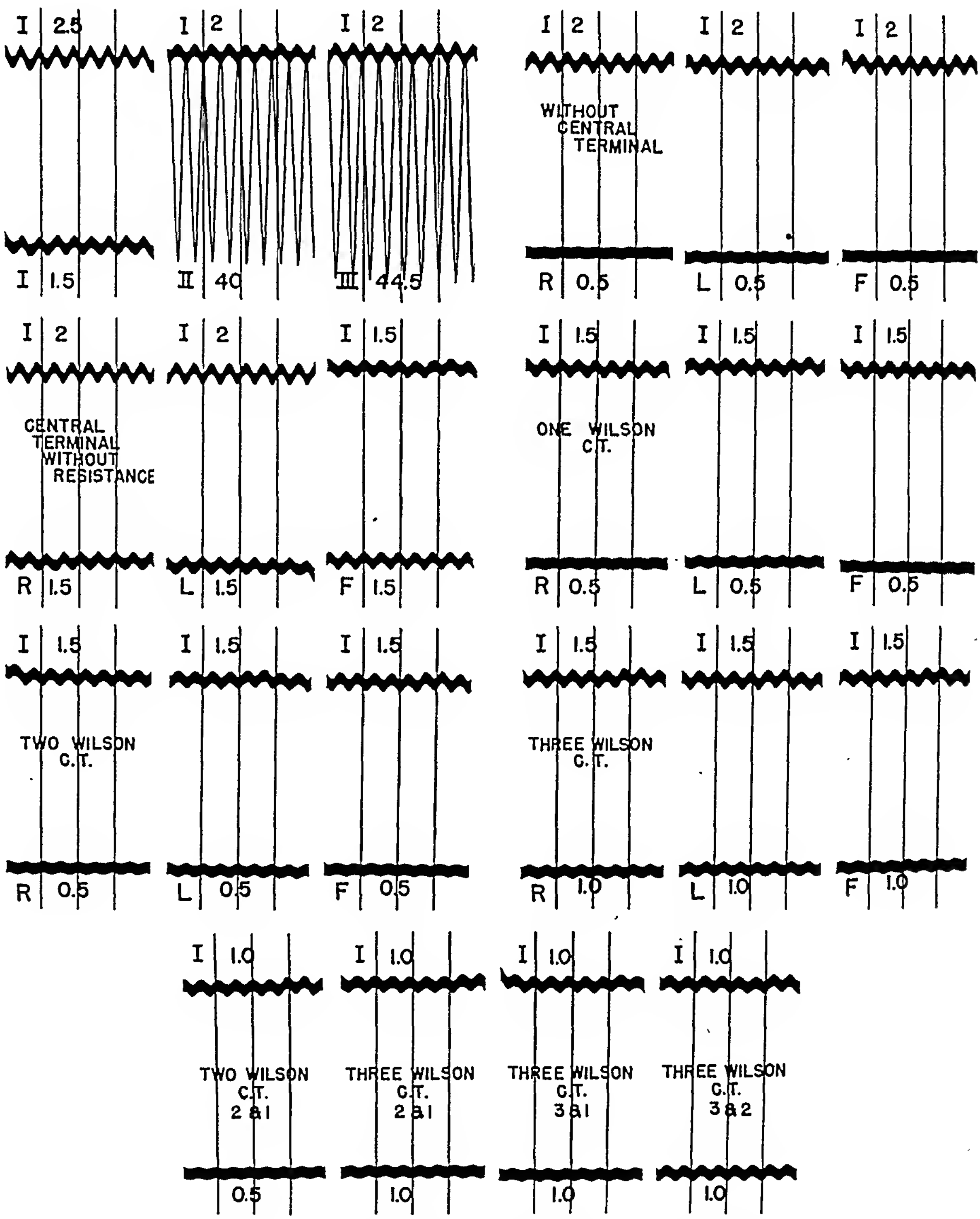

Fig. 2.—Experiment 1. Records of potential differences produced by introducing a small 25 cycle current into the body of a normal subject. Leads R, L, and F are leads from the *A* to the *B* electrodes on the right arm, left arm, and left leg, respectively. The leads at the bottom of the figure show the differences in potential between the various central terminals. Lead I was taken simultaneously with each of the other leads used. Arabic numerals give the amplitudes of the deflections in millimeters. The electrocardiograph was used at its normal sensitivity.

Experiment 2.—In order to obtain larger deflections a second experiment was performed in which the maximal current (0.5 milliampere) which the oscillator was capable of producing was employed. At the same time, the distance between the input electrodes was made as large as possible so as to give the electrical moment, which is measured by the product of the current and the distance between the electrodes, the greatest value attainable. In addition, the records were taken with the electrocardiograph operating at double its normal sensitivity. Under these circumstances the potential variations of the extremities were naturally of such great magnitude that it was impossible to record the deflections in Leads II and III. The potential differences between the Electrodes *A* and *B* and between the central terminals were recorded exactly as in Experiment 1.

The tracings obtained are reproduced in Fig. 3. Before any of the distal electrodes were joined to a central terminal the deflections in Leads R, L, and F, which are a measure of the currents flowing in the extremities, were slightly larger than those recorded in our first experiment under the same circumstances, but still extremely small. They became very large, however, when a central terminal was connected, without intervening resistors, to the limb electrodes of Set 1. The increased flow of current along the limbs was accompanied by a 50 per cent increase in the voltage of the deflections of Lead I. It will be noted that the large current in the leg (*F*) was 180 degrees out of phase, while the currents in the two arms (*R* and *L*) were in phase, with the potential differences which this lead recorded. Since the line joining the input electrodes was nearly parallel to the long axis of the trunk, the potential of the left leg was positive when the potentials of the two arms were negative, and vice versa. Consequently, the leg current was flowing toward the central terminal when the arm currents were flowing away from it, and conversely. It should be noted that the relative amplitude of the oscillations in Leads R and L measures the relative magnitude of the *IR* drops between the *A* and *B* electrodes on the two arms and not necessarily the relative magnitude of the currents flowing in these extremities. There is, however, little question that in this particular instance the current in the left arm was considerably larger than that in the right; this was the cause of the increased voltage of the deflections in Lead I.

When a central terminal with resistances of 5,000 ohms was substituted for the central terminal without resistances, the deflections in Lead I decreased to their original size; the amplitude of the oscillations in Lead R fell from 6.0 to 3.0 mm.; that of the oscillations in Lead L, from 16 to 3 mm.; and that of the oscillations in Lead F, from 30 to 8 millimeters. When a second, and then a third, central terminal with resistances were connected, these oscillations became larger again, particularly in Leads R and F. The failure of the current in the left arm to increase more than it did when the second and third terminals were added is rather surprising; it may be that the resistances of the areas of skin beneath the Number 2 and Number 3 electrodes on the left arm were large in comparison with the skin resistances beneath the corresponding electrodes on the other extremities. It will be noted that the disproportionate increase in the

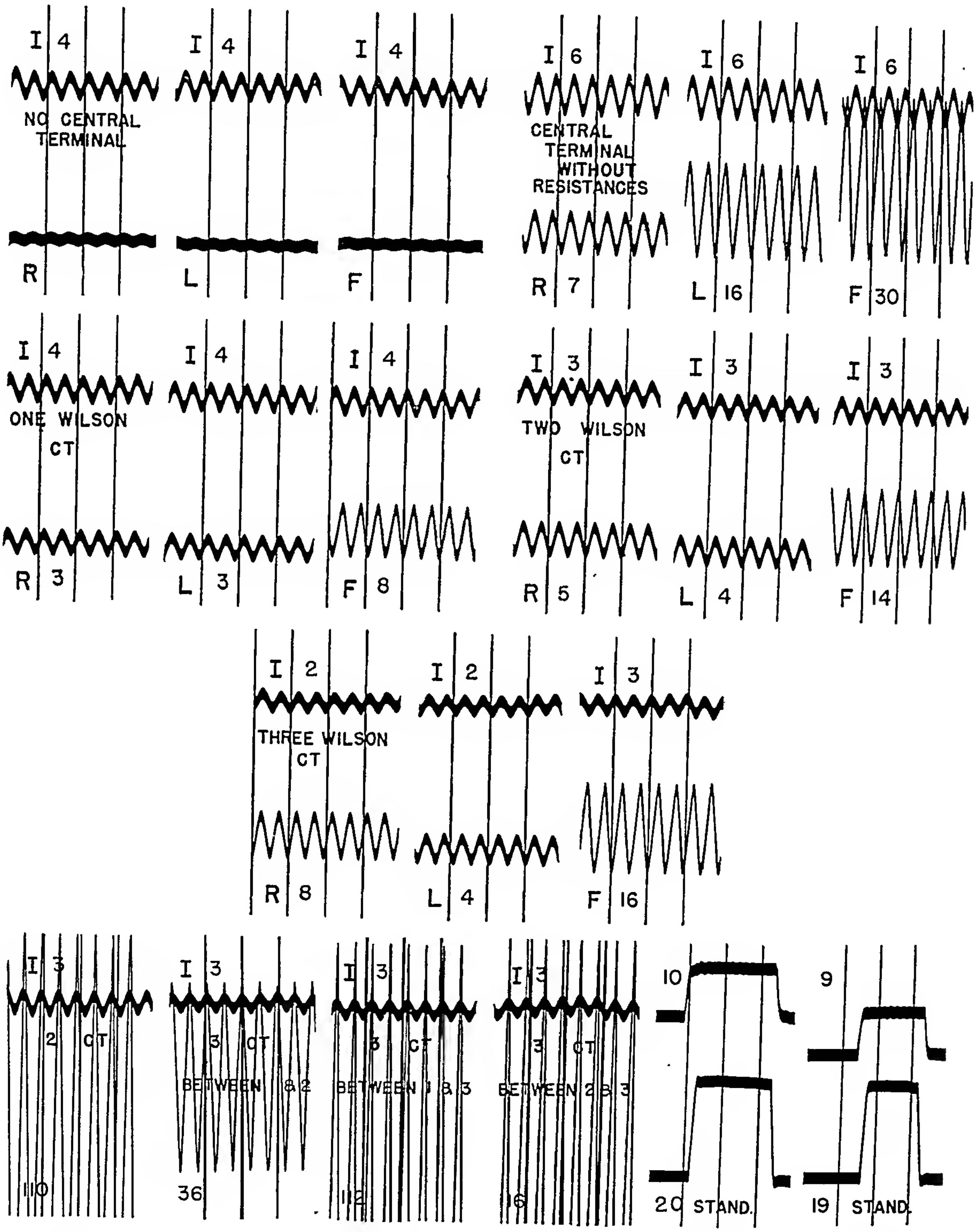

Fig. 3.—Experiment 2. The leads are the same as those shown in Fig. 2. The current and the distance between the input electrodes were adjusted to give the maximal electrical moment attainable. The lower beam was standardized at double the normal sensitivity. Arabic numerals give the amplitude of the deflections in millimeters. The last two strips show standardization before and after the experiment and demonstrate a very slight change in the sensitivity of the electrocardiograph.

current in the right arm as compared to that in the left was accompanied by a reduction in the size of the deflections in Lead I.

All of the potential differences between the central terminals, with one exception, were so large that they could not be satisfactorily recorded. The last two strips of record in Fig. 3 show the effect of throwing a millivolt into the electrocardiographic circuit at the beginning of the experiment, and again at the end. The sensitivity of the instrument decreased slightly during the interval which elapsed between the two tests.

DISCUSSION

It is evident that the phenomena described were dependent, in one way or another, upon the absolute and relative magnitudes of the resistances, or other parameters, of the circuits established by connecting one or more central terminals to the electrodes on the limbs. The circuit elements referred to are indicated in the diagram reproduced in Fig. 4. The five electrodes, A, B, *1*, *2*, and *3*, on each of two extremities are shown, together with the resistances, R_a, R_b, R_1, and so forth, between them and the internal tissues. The resistances of the internal tissues of the segments of the extremities between the various electrodes and between the A electrodes and the poles of the battery E_1, which represents the open-circuit potential difference between the two extremities, have been assigned the symbols r_a, r_b, r_c, and so forth. To avoid complications the third extremity is not included in the diagram. When it is necessary to distinguish between the circuit elements of one extremity and those of another, we shall use unprimed symbols when referring to circuit elements associated with the right arm, primed symbols for the corresponding elements associated with the left arm, and double-primed symbols for those associated with the left leg. The symbols A, A', and A'', for example, refer to the A electrodes on the right arm, left arm, and left leg, respectively. For the equal resistances in the branches of the central terminal we shall use the symbol R.

The circuit diagram of Fig. 4 is very much like that of a Wheatstone bridge, but has three branches connected in parallel instead of only two. These are the branches in which the central terminals lie. It is clear that the voltage drop in each of them is equal to the difference in potential between the nodes X and X'. The potential of each of the central terminals, with reference to that of either of these nodes, is determined by the ratio of the two resistances (or sums of resistances) which separates the one from the other. The potential of the terminal connected to the two Number 1 electrodes is, then, determined by the ratio $(R+R_1):(R+R'_1)$; that of the terminal connected to the Number 2 electrodes, by the ratio $(R+R_2+r_d):(R+R'_2+r'_d)$; and that of the terminal connected to the Number 3 electrodes, by the ratio $(R+R_3+r_e+r_d):(R+R'_3+r'_e+r'_d)$. When these three ratios are equal, the three terminals are necessarily always at the same potential, and when any two of them are equal, the potentials of the corresponding terminals are equal. If the two equal resistances R are very large in comparison with the differences in magnitude between the members of each of the other pairs of resistances involved, the differences in potential

between the three central terminals will be negligible. The members of the pairs of skin resistances, R_1, R'_1; R_2, R'_2; and R_3, R'_3, are those most likely to be unequal, for the skin resistance is usually high in comparison with the resistance of the internal tissues and is to a large extent dependent upon the technique used

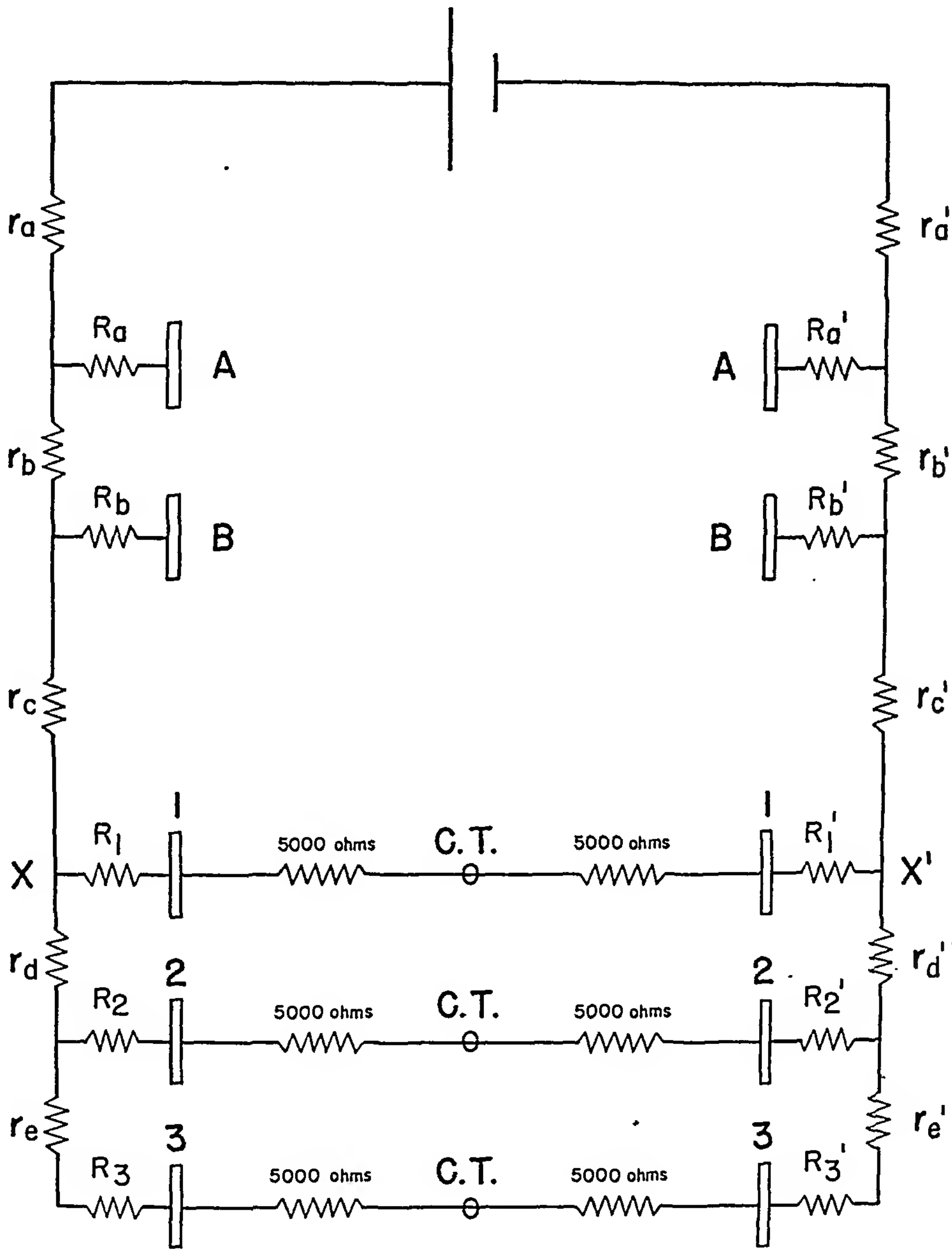

Fig. 4.—Schematic representation of the electrical circuits established by connecting three central terminals to separate sets of limb electrodes on two extremities. *r*, resistance of internal tissues; *R*, resistance of skin beneath electrode; *CT*, central terminal; *A* and *B*, electrodes used to estimate changes in current flowing along extremity; *1*, *2*, and *3*, sets of limb electrodes attached to the three central terminals. For the sake of simplicity the third extremity is not shown in the diagram. See text for further details.

in attaching the electrodes to it. It would, of course, be possible to measure the resistances between the limb electrodes of each set and then equalize them by adding the appropriate resistances to the arms of each of the central terminals.

This procedure would insure that all of the central terminals would be at the same potential.[2]

When each of the different central terminals is connected to three limb electrodes instead of two the situation is considerably more complicated, but the principles involved are the same. There are then three nodes, X, X', and X'', and the potential of each terminal with respect to them is determined by two ratios. In the case of the terminal connected to the Number 1 electrodes, these ratios are defined by the expression $(R + R_1):(R + R'_1):(R + R''_1)$. The corresponding ratios for the other terminals are the following:

$(R + R_2 + r_d):(R + R'_2 + r'_d):(R + R''_2 + r''_d)$ and

$(R + R_3 + r_d + r_e):(R + R'_3 + r'_d + r'_e):(R + R''_3 + r''_d + r''_e)$.

If these ratios are equal the potentials of all three terminals must be the same.

The Leads R, L, and F in our experiments recorded the voltage drops across the resistances r_b, r'_b, and r''_b, respectively. Consequently, the deflection in each of these leads represents the product of the corresponding resistance and the current flowing through it. Since the resistances involved are those of the internal tissues, it may be assumed that they did not vary. The currents, on the other hand, were determined by the ratios of the voltages acting in the respective circuits to the total resistances in these circuits. When the resistances between the limb electrodes are equal the equations which define the currents in the branches of the central terminal, and therefore in the extremities to which they are connected, are of the following type:

$$i_F = \frac{E_2 + E_3}{R_T + 3R_F + 3R}$$

Here i_F is the current in the left leg; E_2 and E_3 are the open-circuit voltages in Leads II and III, respectively; R_T is the resistance of the trunk; R_F is the total resistance of the left leg, and therefore represents the sum of the skin resistance and the resistance of the inner tissues; and R is the value of the equal resistances in the branches of the central terminal.

It is obvious that when R is large the currents in the extremities are small. When it is very large in comparison with the resistances in the limb leads, each of which is the sum of the resistances of two extremities plus the resistance of the trunk, the current in a given limb will be strictly proportional to the algebraic sum of the open-circuit voltages in the two standard limb leads in which that limb is attached to the electrocardiographic terminals. In this case inequalities of the skin resistances will have no significant effect upon the potential of the central terminal. When R is small the opposite will be the case. The flow of current through the extremities will be large, and this will not only increase the effects in question but may give rise to others due to polarization in the skin. What may happen when the resistances in the arms of the central terminal are dispensed with is, therefore, unpredictable. Connecting three central terminals to separate sets of electrodes may be expected to have about the same effect upon the size of the currents in the limbs as that produced by reducing the magnitude of resistances in the arms of the central terminal by two-thirds.

CONCLUSIONS

It is true that, under certain circumstances, multiple central terminals each connected to a separate set of limb electrodes are not at the same potential. The differences in potential between them are due to inequalities in the resistances between the limb electrodes to which they are attached, and these in turn are probably due chiefly to inequalities in the resistances of the areas of skin beneath these electrodes.

These differences in potential will not occur if the resistances between the limb electrodes are measured and equalized, or if the resistances in the arms of the central terminals are sufficiently large.

The phenomena in question do not have an important bearing upon the validity of the Einthoven triangle or upon the usefulness of the central terminal as a reference electrode. They do indicate that the resistances in the arms of the central terminal should be as large as practicable.

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CLINICAL STUDIES ON TWENTY-ONE CASES OF COARCTATION OF THE AORTA

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THE success of surgical treatment of coarctation of the aorta stimulated this study of the clinical data in twenty-one cases. It is obvious from a study of the literature that the diagnosis of coarctation is still frequently missed. Abbott[1] in 1928, in her report on 200 autopsied cases, found a correct clinical diagnosis in only twenty-eight (14 per cent), while Reifenstein, Levine, and Gross[2] in 1947 found that a correct clinical diagnosis had been made in forty-two (40 per cent) of their 104 cases. A number of other current articles[3,4] point out the frequency with which the correct diagnosis is overlooked.

Patients with coarctation of the aorta seldom consult a physician because of symptoms. Most cases are found accidentally during routine examination. Others are referred for cardiac study because of a murmur heard over the heart. The absence of symptoms, however, is misleading. While most of these individuals are in apparent good health, the majority die in early life. In Abbott's series,[1] 74 per cent, and in the series reported by Reifenstein and co-workers,[2] 61 per cent died before or during their fortieth year of life. The average age at death was 35 years.

The present study was undertaken primarily to determine the reasons for failure to make an early correct diagnosis and also to observe the progress of the disease in patients followed from childhood for a number of years. It was hoped that examination of the clinical data might help in determining which patients should be treated surgically. Of the twenty-one patients who have come under my observation, twelve have been studied from one to five years; five, from five to ten years; and four, for ten years or more. As in all other series, the male sex predominates. In this group there were three female and eighteen male patients. In only three cases was the correct diagnosis made before the patient was seen in the clinic. In one case an abnormal shadow found during the routine chest x-ray survey led to the correct diagnosis. In all other instances, the patients were referred for cardiac study either because it was known that the child had had a cardiac murmur since birth or because of a murmur found during routine school physical examination.

Age of Patients.—When first examined, seventeen of the patients were under 20 years of age; twelve were under 10; in one the diagnosis was made at 2 years

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of age. Five were between the ages of 20 and 45. One was first examined at 67 years of age. He is now 72 years old and is in cardiac failure, but had been in excellent health until two years ago.

Murmurs.—A systolic murmur over the apex and over the aortic area is commonly heard in coarctation of the aorta. Usually this murmur is loudest over the aortic area. Occasionally a typical machinery murmur is heard over the pulmonic area, indicating an accompanying patent ductus arteriosus. Diastolic murmurs heard along the left border of the sternum or over the aortic area indicate aortic regurgitation commonly secondary to a bicuspid aortic valve, an anomaly which occurs in 30 to 40 per cent of the cases of coarctation. In our series, we found seventeen patients with a systolic murmur at the apex, twenty with a systolic murmur over the aortic area, three with an accompanying diastolic murmur, and one with a machinery murmur (Table I). In one case no murmur was heard over the heart. There is nothing characteristic about the systolic murmur heard over the anterior chest. There is, however, a more definitely diagnostic murmur commonly heard over the back on either side of the vertebral column and around the area of the angle of the scapulae and in the axillae. This is a superficial vascular murmur which is generated in the enlarged collateral vessels. The detection of this murmur, particularly in young patients, was often the first clue which led to a correct diagnosis. This murmur is loudest over the enlarged vessels and diminishes in intensity as the bell of the stethescope leaves this area. The murmur increases in intensity again as one nears the next enlarged vessel. Not infrequently the murmur in the back is louder than the murmur over the heart.

TABLE I. TYPE AND LOCATION OF MURMURS

SYSTOLIC			DIASTOLIC	MACHINERY
APEX	AORTIC AREA	BACK		
17	20	20	3	1

In one case no murmurs were heard over the heart.

Size of the Heart.—Hypertrophy of the left ventricle is a common finding in coarctation of the aorta. The enlargement of the left ventricle, however, is not as great as one would expect. The heart is more often enlarged in those patients with higher blood pressures. However, in some cases, as has been pointed out by other investigators,[3,4,5] patients with very high blood pressure, even though followed over many years, fail to show any considerable increase in the size of the left ventricle. Case 1 (Tab'e II) is an example of this type. This young man, first examined at the age of 18 and followed for two years, has a systolic blood pressure of over 200 mm. Hg, yet has no apparent enlargement of the heart. In those of our patients who have been observed from early childhood there is a gradual increase in the size of the heart. In two patients (Cases 2 and 3) marked

TABLE II. HEART SIZE, DEGREE OF EROSION OF RIBS, BLOOD PRESSURE, AND AGE IN TWENTY-ONE PATIENTS WITH COARCTATION OF AORTA

CASE NO.	EROSION OF RIBS		SIZE OF HEART		BLOOD PRESSURE ARM		BLOOD PRESSURE LEG		AGES FOLLOWED	NO. YRS. FOLLOWED
	FIRST EXAM.	LAST EXAM.	FIRST EXAM.	LAST EXAM.	FIRST EXAM.	LAST EXAM.	FIRST EXAM.	LAST EXAM.		
1. (D)	0	0	0	0	214/80	226/100	148/90	148/84	18–20	2
2. (Ab)*	+	+	++	++	150/100	150/104	0	0	6–10	4
3. (JM)†	++	++	++	++	176/130	160/120	0	0	6–12	6
4. (BL)†	0	+	+	+	106/50	140/70	0	0	6– 7	1
5. (Hol)	0	0	0	+	140/90	190/140	90?	100?	11–18	7
6. (Mor)	0	+	0	0	114/86	158/78	?	?	6–22	16
7. (Bj)	0	0	0	0	148/108	150/80	0	0	8–16	8
8. (Carl)*	+	++	0	+	150/110	190/124	0	0	7–26	19
9. (Berg)*	0	0	+++	+++	206/60	190/60	0	0	25–26	1
10. (St)	0	0	0	0	110/70	120/80	0	0	2– 3	1
11. (Jam)	0	0	+	+	110/90	124/88	0	0	13–23	10
12. (ST. C.)	0	0	0	0	130/40		110/74		7–11	4
13. (01)	+	+	0	0	112/80	118/70	70?	68?	8–11	3
14. (Ha)	++	++	+	++	114/100	160/108	100/90	0	6–22	16
15. (Joh)	+	+	+++	+++	150/100	130/80	110/100	?	36–37	1
16. (Ry)*	++	++	++	++	160/100	160/100	0	0	20–20	0
17. (Cl)*†	+	++	++	++	140/90	192/101	0	0	7–10	3
18. (Ly)	0	?	+	++	124/90	150/100	0	0	5– 6	1
19. (O'B)†	+	++	+	++	148/68	138/80	0	0	12–18	6
20. (Wal)	+++	+++	+++	+++	180/90	190/100	0	?	43–46	3
21. (Sm)	++	++	+	++	168/84	178/88	?	?	67–72	5

*Deceased.
†Operated.

left ventricular enlargement was present at 6 years of age. In ten patients there is either no enlargement or merely slight left ventricular enlargement. In six of these there is, nevertheless, marked hypertension (Cases 1 and 4 to 8). The patient with the largest heart in our group had in addition to a marked coarctation a rheumatic aortic regurgitation and stenosis (Case 9).

Blood Pressure.—The most significant clinical finding in coarctation of the aorta is the increased blood pressure in the arms with a diminished pressure in the lower extremities. Hypertension, however, does not always occur. A study of the blood pressure readings in our cases reveals that among the younger patients the pressure gradually increases. However, in several instances (Cases 10 to 13), the blood pressure has remained within normal limits during the period of observation. In five patients (Cases 2, 3, 4, 7, and 8) there was a definite increase in blood pressure at the early age of 6 or 7 years. There does not appear to be a good correlation between the height of the pressure and the grade of coarctation. The difference between the height of the pressure in the arms and that in the legs seems more important. Considerable difference between the blood pressure in the upper and lower extremities usually indicates a high grade aortic obstruction.

Collateral Circulation.—A child born with coarctation of the aorta will gradually develop collateral circulation as the ductus arteriosus closes. When the collateral blood is supplied by the greatly enlarged intercostal vessels, erosion of the ribs results. When this occurs, it produces a roentgen picture which is pathognomonic. However, when the bulk of the collateral circulation takes a route other than through the intercostals, no erosion of the ribs will occur.[6,7]

In our series, thirteen patients, when last examined, had erosion of the ribs of varying degree. In ten of our younger patients, no erosion was present when they were first examined, but it gradually developed during the years of observation. Four patients (Cases 2, 3, 4, and 14) had well-advanced erosion of the ribs at the early age of 6 years. For instance, Case 14, a young man who is now 22 years of age, was examined first at the age of 6 years. It will be noted (Fig. 1) that he already has marked erosion of the ribs. Now at the age of 22, the erosion of the ribs is much more advanced (Fig. 2). Case 3 was first examined at the age of six when he had far advanced erosion of the ribs (Fig. 3). Now at the age of 12, the erosion of the ribs has progressed further (Fig. 4). It is obvious that when extensive erosion of the ribs can be observed at the age of 6, this process must have had its inception some years previously.

When erosion of the ribs occurs in the young individual, one can conclude that marked constriction of the aorta is present. However, far advanced coarctation of the aorta does occur without any evidence of erosion of the ribs. The following case is a good example of this type:

Case 9, a young man of 26 who died in cardiac failure, was found to have a tremendously enlarged heart and high grade coarctation of the aorta with an

Fig. 1.

Fig. 2.

Fig. 1.—Well-advanced erosion of the ribs at the age of 6 years.

Fig. 2.—More marked erosion of the ribs in the same patient at the age of 22 years.

Fig. 3.

Fig. 4.

Fig. 3.—Far-advanced erosion of the ribs and marked enlargement of the heart at the age of 6 years.

Fig. 4.—More marked erosion of the ribs at the age of 12 years. Note also the shadow of the enlarged left subclavian artery.

accompanying rheumatic aortic lesion, yet his x-ray film shows only questionable erosion of the ribs (Fig. 5).

Another characteristic finding on the x-ray film[8,9] results from the marked enlargement of the left subclavian artery. This vessel enlarges tremendously and in some instances is as large as the aorta. The enlarged subclavian artery has frequently been mistakenly interpreted as the aortic knob. The aortic knob, however, in coarctation is usually not prominent. This is due to the fact that it is pulled downward and medially by traction of the ligamentum arteriosum so that the aortic knob is frequently behind the sternum. The enlarged subclavian artery produces a shadow which is sometimes in the usual location of the aortic knob. This results in either a localized rounded shadow or in an increased widened area over the entire upper left border of the heart. Detection of this enlarged artery by the roentgenologist, especially where there is no accompanying erosion of the ribs, could lead to a correct diagnosis. There was an enlarged left subclavian artery in the roentgen film in nine of our cases. Fig. 6 presents a good example of this type.

Causes of Death.—The common causes of death in coarctation of the aorta are rupture of the aorta, bacterial endocarditis or endarteritis, congestive failure, and intracranial hemorrhage usually resulting from congenital aneurysm of the cerebral vessels.

Five of our patients have died (Cases 2, 8, 9, 16, and 17). A 20-year-old man and a 10-year-old boy died of cerebral hemorrhage, and a 26-year-old man probably died of cerebral hemorrhage. A 10-year-old boy died following surgery and a 26-year-old man died of cardiac failure. In the four patients on whom post-mortem examination was done, all were found to have had either complete atresia or high grade coarctation of the aorta.

Results of Surgery.—By examining the current literature and through personal correspondence, I have obtained information on 128 patients who have been operated upon for coarctation of the aorta. Of this number, twenty (16 per cent) (Table III) died during or soon after operation. Unfortunately, the result was not satisfactory in all the surviving patients. In ninety-three individuals it was possible to complete an aortic anastomosis. In eighteen the left subclavian artery was anastomosed to the aorta. This was necessary because an end-to-end anastomosis was technically impossible either because the constricted area in the aorta was too extensive or because the left subclavian artery arose too close to the localized area of constriction. In several older patients, extensive atherosclerosis made aortic anastomosis impossible. With few exceptions, the results following subclavian-aortic anastomosis have been unsatisfactory. Using the subclavian artery apparently does not reduce the load to the upper part of the body, nor does it increase the amount of blood to the lower half. This procedure does not give favorable results and will undoubtedly be abandoned.

Fig. 5.—Patient, age 26, found to have marked coarctation of the aorta with rheumatic aortic disease. Marked cardiac enlargement with minimal erosion of the ribs.

A better selection of patients for operation by the diagnostician will give more favorable results. It is hoped that the newer methods[10] of visualizing the aortic arch by direct arterial injection of a radiopaque substance will help in avoiding operation on patients in whom the anatomical relationships are such that aortic anastomosis is impossible.

Fig. 6.—Marked enlargement of the left subclavian artery. Aortic arch shown below the shadow of the left subclavian artery.

Some of the surgical deaths occurred in older patients where the surgeon met with extensive atherosclerosis making satisfactory anastomosis very difficult and in some instances impossible. Other fatalities resulted from inexperience. A much better record can be expected as surgeons gain more experience.

TABLE III. RESULTS AND TYPE OF OPERATION IN ONE HUNDRED TWENTY-EIGHT PATIENTS WITH COARCTATION OF AORTA

NUMBER OF SURGEONS	NUMBER OPERATED	NUMBER OF DEATHS	PER CENT DEATHS	AORTIC ANASTOMOSIS	SUBCLAVIAN AORTIC ANASTOMOSIS
13	128	20	16	93	18

Four of our patients have been operated upon (Cases 3, 4, 17, and 19). They were all under 18 years of age. One died of acute pulmonary edema as he was being lifted off the operating table. All four had successful aortic anastomosis performed. The result was excellent in the three surviving patients.

DISCUSSION

It was hoped that this study might result in the development of a typical clinical syndrome which would make the diagnosis of coarctation of the aorta much simpler and thereby reduce the percentage of error. Unfortunately, the various factors involved do not correlate well. In the typical case with hypertension, erosion of the ribs, and left ventricular hypertrophy, the diagnosis should be readily made. In those cases, especially in the young individual, where one or more of these findings are not present, the diagnosis is more difficult and will depend on a careful physical examination. Inspection and palpation of the back will be rewarded by the finding of enlarged collateral vessels. Auscultation of the back in all cardiac patients will prevent overlooking coarctation. Routine palpation of the abdominal and femoral pulses, together with systematic blood pressure determinations in the arms and legs, particularly in children, will tend to avoid error. Particular attention should be given to all patients with hypertension, aortic regurgitation, patent ductus arteriosus, and spontaneous subarachnoid hemorrhage. It is among this group that coarctation of the aorta is most frequently overlooked.

No fixed rule for surgical intervention can be offered. In the young patients with all the typical findings, surgery is of course indicated. In young individuals with definite evidence of high grade coarctation, even though no marked hypertension or enlargement of the heart is present, surgery should be seriously considered. In individuals beyond the age of 20 years, surgical treatment is much

more hazardous and should probably be delayed until surgeons gain more experience. Such experience might better be secured by operating successfully on more younger patients than by courting disaster in attempting surgery on older individuals. With the present successful treatment of coarctation, it is most unfortunate when the diagnosis is missed in early childhood. If surgical treatment is limited to young individuals, preferably between the ages of 10 and 20 years, the results will be exceedingly satisfactory and the mortality rate should be reduced to the 1 per cent which has been attained in surgery for patent ductus arteriosus.

CONCLUSIONS

1. The diagnosis of coarctation of the aorta is still frequently missed. This is particularly true in young patients who do not reveal an increased blood pressure in the upper extremities and do not have erosion of the ribs.

2. Careful clinical study including inspection and palpation of the back for enlarged collateral vessels as well as auscultation over these enlarged vessels will prevent errors in diagnosis.

3. Routine blood pressure determinations in arms and legs as well as routine palpation of the femoral pulse will lead to a correct diagnosis.

4. The clinical findings in twenty-one patients have been described.

5. An incomplete study of the results of surgery up to the present time has been presented.

6. The results of surgery and the cause of death among our patients have been discussed.

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A CLINICAL STUDY OF SUBACUTE BACTERIAL INFECTION CONFINED TO THE RIGHT SIDE OF THE HEART OR THE PULMONARY ARTERY

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SUBACUTE bacterial endocarditis involves the left side of the heart in nearly all cases. The complete descriptions of the disease by Libman and Friedberg,[1] Blumer,[2] and Middleton and Burke[3] refer chiefly to this common type. The vegetations are confined to the right side of the heart in less than 4 per cent of the cases.[4,5] In patent ductus arteriosus complicated by subacute bacterial endarteritis the vegetations are sometimes confined to the ductus, pulmonary artery, and pulmonic valves. Although some of the features of the right-sided type of the disease have been pointed out, notably by Gordon,[6] Libman and Friedberg,[1] Lutembacher,[7,8] and Blumgart,[9] it has not been described adequately. The purpose of this paper is to present a review of the clinical findings in cases proved by autopsy to have vegetations confined to the right side of the heart or the pulmonary artery.

MATERIAL

A search of the literature revealed thirty-six cases in which the data were sufficiently complete for the purposes of this study. To these are added five additional cases observed at the University Hospital, bringing the total to forty-one cases. Other cases have been reported in the literature, but are not included because the descriptions, particularly from the clinical standpoint, are not sufficiently complete. Similarly, the cases of patients with patent ductus arteriosus with superimposed subacute bacterial infection who recovered following ligation or section of the ductus are not included; although the infection was presumably limited to the right side in most if not all of them, this could not be determined with certainty. Cases of acute bacterial endocarditis are not included.[10] Some of the reports deal with particular features of the disease and are incomplete in many respects, but in spite of this it is hoped that this report will present an adequate clinical description of the right-sided type of subacute bacterial endocarditis.

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REPORT OF CASES

CASE 1.—V. S., a 13-year-old white boy, was admitted to the hospital Feb. 6, 1939, and died Feb. 12, 1939. At the age of 3 weeks the patient had a severe cough and the parents were told that it was caused by heart disease. At 3 months of age he became extremely ill with high fever and was kept in the hospital for eight months. At 3 years of age he developed hay fever, which was accompanied by cough and which was worse in summer. In January, 1938, he began having chills and fever. He was somewhat improved after twelve weeks, but low-grade fever persisted. In October, 1938, the chills recurred and the fever became higher. On Jan. 23, 1939, he developed swelling of the left eyelids. On Feb. 5, 1939, he developed swelling of the left foot and gangrene of the pinnae of the ears and tip of the nose. Numerous small red spots appeared in the skin. He had anorexia, nausea, and vomiting. There was no history of rheumatic fever.

Physical examination revealed a pale, emaciated boy with a temperature of 102° F., pulse rate of 132, and respiratory rate of 30. There were small areas of ulceration on the pinnae of the ears and tip of the nose. Numerous petechiae were present on the trunk and extremities. The heart was moderately enlarged and the rhythm regular. There was a loud systolic murmur over the entire precordium and a questionable diastolic murmur in the aortic area. The lungs were resonant and there were no râles, but the breath sounds were diminished at the bases. The spleen was enlarged and palpable; the liver was not felt. There was no edema.

Laboratory examinations revealed the following findings: The urine contained a moderate amount of albumin and a few red cells, white cells, and casts. The blood revealed a hemoglobin of 20 per cent, a red blood cell count of 1,620,000, and a white blood cell count of 7,000, with 74 per cent polymorphonuclear leucocytes. The blood culture was positive for *Streptococcus viridans.*

The course was progressively downward in spite of small blood transfusions daily.

Necropsy showed congenital heart disease with a large defect in the interventricular septum and hypertrophy of the right ventricle. There was subacute bacterial endocarditis with vegetations on the tricuspid and pulmonic valves, on the mural endocardium of the right ventricle, and on the margin of the septal defect. There were no vegetations in the left side of the heart. There were infected pulmonary emboli and pulmonary infarcts, acute pulmonary edema, acute purulent bronchitis, acute fibrinopurulent lobular pneumonia, and bronchiectasis. There were healed and healing infected infarcts of the spleen, which weighed 400 grams, and recent healing and healed embolic glomerulitis.

CASE 2.—W. W., a 25-year-old white man, was admitted to the hospital Nov. 9, 1926, and died Dec. 17, 1926. Dyspnea and palpitation occurred upon exertion during childhood and heart disease was recognized. Nevertheless, he was accepted for life insurance at the age of 17 years. In November, 1925, he developed dyspnea upon exertion and fatigue and began losing weight. In February, 1926, he developed increasing dyspnea and palpitation and stopped work. In April, 1926, he developed cough productive of a little sputum, but no blood. Edema of the ankles appeared in May, 1926. There was no known fever and no history of rheumatic fever or venereal disease.

The physical examination revealed a thin, pale, slightly cyanotic young man with clubbing of the fingers but no petechiae. The heart was enlarged and the rhythm regular. There was a loud, harsh systolic murmur accompanied by a thrill in the second intercostal space to the left and right of the sternum and a softer systolic murmur at the apex, but no diastolic murmur. The blood pressure was 106/54. The lungs were clear, the spleen was palpable, and there was slight edema of the ankles.

Laboratory examinations revealed a negative Wassermann. The urine showed a trace of albumin, moderate numbers of red cells, and a few white cells. The blood revealed a hemoglobin of 60 per cent, a red blood cell count of 3,310,000, and a white blood cell count of 16,200, with 91 per cent polymorphonuclear leucocytes. X-ray films of the chest showed enlargement of the heart and densities in the lungs suggesting infarcts or bronchopneumonia. The electrocardiogram showed right axis deviation. Blood cultures were positive for *Streptococcus viridans.*

The course was progressively downward. The temperature fluctuated from 97 to 102° Fahrenheit. Râles and bronchovesicular breath sounds appeared over the right lung. No petechiae or systemic emboli were recognized.

Necropsy showed congenital pulmonary stenosis and subacute bacterial endocarditis with vegetations on the pulmonic and tricuspid valves. There were vegetations and an early mycotic aneurysm in the first part of the pulmonary artery. There were no vegetations or valve lesions in the left side of the heart and no abnormal communication. There were multiple large infarcts of the lungs and multiple small infarcts of the kidneys. There was hyperplasia of the spleen, which weighed 230 grams, but no infarcts.

CASE 3.—N. B., a 48-year-old East Indian man, was admitted to the hospital Jan. 19, 1938, and died March 15, 1938. The history revealed that for four months the patient had experienced chills, fever, sweats, cough, bloody sputum, pains in the chest and left shoulder, anorexia, and loss of fifty pounds in weight.

Physical examination revealed a pale, emaciated, and dyspneic man with slight cyanosis and clubbing of the fingers, but no petechiae. The heart was slightly enlarged, the rhythm was regular, and no murmurs were detected. The blood pressure was 85/50. There were a few râles at the lung bases. The liver and spleen were not felt. There was no edema.

Laboratory examinations revealed the following findings: The Kahn reaction of the blood was negative. The urine showed a large amount of albumin and a few red cells and white cells. The blood revealed a hemoglobin of 55 per cent, a red blood cell count of 2,380,000, and a white blood cell count of 16,500, with 81 per cent polymorphonuclear leucocytes. X-ray study of the chest showed slight enlargement of the heart, but no abnormality of the lungs. The electrocardiogram showed slight left axis deviation. The total serum proteins were 4.5 per cent, albumin 1.6 per cent, and globulin 2.9 per cent. The blood nonprotein nitrogen was 68.1 mg. per cent. Blood cultures were sterile on four occasions.

The course was progressively downward, apparently without change in physical signs. The temperature fluctuated between 94° and 106° Fahrenheit. Sulfanilamide and four blood transfusions were given.

Necropsy showed ulcerative and vegetative endocarditis of the pulmonary valve and of the walls of the right ventricle and pulmonary artery. The other valves and the left side of the heart were not involved and there were no abnormal communications. There was a large infected embolus in the left pulmonary artery and infarction of the lower lobe of the left lung. There was chronic passive congestion of the spleen. Chronic glomerulonephritis was present. No systemic emboli were discovered.

CASE 4.—M. B., a 3-year-old white girl, was admitted to the hospital Oct. 14, 1932, and died Nov. 11, 1932. The patient was thought to have congenital heart disease since a cardiac murmur had been present since infancy. For four weeks prior to admission the child had a cold, a sore throat, chills, fever, cough, and constipation.

Physical examination showed a well-developed and well-nourished child with pallor but no petechiae and no clubbing of the fingers. The heart was enlarged and there was a systolic murmur heard over the entire precordium and loudest at the apex. The lungs were clear. The liver and spleen were not felt. There was no edema.

Laboratory examinations revealed a negative Kahn reaction of the blood. The urine showed a few white cells but was otherwise negative. Blood studies revealed a hemoglobin of 66 per cent, a red blood cell count of 4,480,000, and a white blood cell count of 21,000 with 77 per cent polymorphonuclear cells. X-ray study of the chest was negative. Blood cultures were reported as follows: October 14, no growth; October 29, slight growth of hemolytic streptococcus; October 31, no growth; and November 7, *Staphylococcus aureus* and a nonhemolytic streptococcus.

The course was progressively downward. The temperature ranged from 101° to 105° Fahrenheit. Râles appeared in the lungs and the spleen became enlarged, but no petechiae or systemic emboli were seen.

Necropsy showed subacute bacterial endocarditis with vegetations on the pulmonary valve and on the wall of the right ventricle. The other valves and the left ventricle were not involved

and there were no abnormal communications. There were infected infarcts and early embolic abscesses of the lungs. There was hyperplasia and passive congestion of the spleen. No systemic embolism was discovered.

CASE 5:—D. C., a 29-year-old white woman, was admitted to the hospital Sept. 15, 1932, and died Oct. 2, 1932. For eight weeks prior to admission the patient had chills, fever, pains in the joints and muscles, anorexia, nausea, vomiting, cough, weakness, and a loss of eighteen pounds in weight.

Physical examination revealed an obese, pale woman with alopecia, but no petechiae or clubbing of the fingers. There was a soft systolic murmur over the entire precordium. No other murmur was heard and there was no enlargement of the heart. The blood pressure was 120/80. The lungs were clear. The liver and spleen were enlarged and palpable. There was no edema.

Laboratory examinations showed that the Kahn reaction of the blood was 4 plus. The urine showed a few red cells and white cells but was otherwise negative. Blood studies revealed a hemoglobin content of 68 per cent, a red blood cell count of 4,040,000, and a white blood cell count of 15,500, with 88 per cent polymorphonuclear leucocytes. X-ray study of the chest showed no abnormality of the heart or lungs. Blood cultures were sterile on two occasions.

The course was progressively downward. The temperature ranged from 97° F. to 105° Fahrenheit.

Necropsy showed subacute bacterial endocarditis of the tricuspid valve. The other valves and the left ventricle were not involved and there were no abnormal communications. There were passive congestion of the lungs and liver, hyperplasia of the spleen, which weighed 470 grams, and chronic glomerulonephritis. There was no evidence of embolism, gonorrhea, or syphilis.

Of the forty-one cases accepted for this study, nine had patent ductus arteriosus, eleven had interventricular septum defect, one had interauricular septum defect, fifteen had vegetations limited chiefly to the pulmonic valve without abnormal communications, and five had vegetations limited chiefly to the tricuspid valve without abnormal communications. The ages of the patients ranged from 3 to 58 years, and the average was 20.6 years. There were eighteen males and twenty-three females. The important features of these cases are presented in the accompanying Tables I-V and are compared or contrasted with the common left-sided type of the disease.

CLINICAL OBSERVATIONS

Murmurs were present in thirty-seven of the cases. In four patients no murmurs were heard. Two of these had vegetations confined chiefly to the pulmonic valve, while in the third they were confined to the tricuspid valve; in the remaining patient a pericardial friction rub was present and no murmur was identified. Thus, 90 per cent of the patients had cardiac murmurs. In seven cases, however, there were systolic murmurs at the apex or base of the heart or over the precordium, such as are commonly heard in patients with fever and anemia, and were not, therefore, suggestive of a cardiac lesion. In the remaining thirty patients, 73 per cent of the entire group, the murmurs were harsh or were accompanied by a thrill or were diastolic in time, and were thought to indicate a cardiac lesion (Table V).

Fever was present in forty cases. In the remaining case the report did not mention the temperature.

Table I. Clinical and Pathological Data in Nine Cases of Patent Ductus Arteriosus With Right-Sided Subacute Baterial Infection

Patient	Age	Sex	Heart	Fever	Lungs	Blood culture	Spleen	Urine	Kidneys	Petechiae	Anemia	Leucocytosis	Systemic embolism	Clubbing	Duration (months)
Abbott[11]	33	M	Rough systolic murmur at base	+	Pain; cough									+	7
Schlaepfer[12]	8	M	Typical murmur	+	Infarcts	+	Infarcts			–	+	+	Spleen		2
Philpott[13]	6	F	Systolic murmur pulmonic area	+	Râles; x-ray; infarcts	+	Enlarged; congestion; hyperplasia	+	Glomerular nephritis	–	+	+	None		6
Gordon and Perla[14]	13	M	Typical murmur	+	Physical signs; infarcts	+	Pain; infarct	– +	Embolic nephritis	+	+		Spleen		3
Blumer and McAlenney[15]	16	M	Typical murmur	+	Pain; cough; infarcts	–	Pain; infarcts	+	Infarcts	+	–	+	Spleen; kidneys	+	2
	8	M	Typical murmur	+	Pain; infarcts	+	Pain; infarcts	+		–	+	+	Spleen		2
Weiss[16]	33	F	Rough systolic pulmonic murmur	+	Physical signs; abscesses	–	Not felt	+		–	+	+	None		2
Hines and Wood[17]	18	F	Typical murmur	+	Pain; hemoptysis; x-ray; infarcts	+	Enlarged; no infarct	– +	Glomerular and embolic nephritis	–	+	+	Kidneys		12
Graybiel and associates[18]	22	F	Typical murmur	+	Pain; hemoptysis; x-ray; infarcts	+	Not felt	+		–	+	+			4

Table II. Clinical and Pathological Data in Twelve Cases With Septum Defects and Right-Sided Subacute Bacterial Infection

Patient	Age	Sex	Heart	Fever	Lungs	Blood culture	Spleen	Urine	Kidneys	Petechiae	Anemia	Leucocytosis	Systemic embolism	Clubbing	Duration (months)
Mayer[19]	16	F	Loud systolic murmur	+	Physical signs; infarcts?		Enlarged; no infarcts	+	No infarcts		+		None	+	6
Tuckwell[20]	4	M	Systolic murmur at apex	+	Physical signs; infarcts		Infarct		Negative		+		Left eye; spleen		1
Mackenzie[21]	21	M	Systolic murmur and thrill		Pain; tuberculosis				Tuberculosis						9
Gordon[6]	5	M	Loud systolic murmur; thrill	+	Physical signs; infarcts		Enlarged	−		−	+		None		2
Horder[22]	7	M	Loud systolic murmur	+		−		− +						+	8
Humphry[23]	18	M	Loud systolic murmur; thrill	+	Physical signs; infarcts	−		+		+		+	None		11
Moschcowitz[24]	29	F	Loud systolic murmur	+	Pain; hemoptysis; physical signs; infarcts	− +	Enlarged; infarcts; hyperplasia; congestion	− +	Glomerular nephritis; infarcts	+			Spleen; kidneys		13
Blumgart[9]	13	F	Systolic and diastolic murmurs and thrills	+	Pain; physical signs; x-ray; infarcts	−	Enlarged; congestion	+	Glomerular nephritis	+	+	+	None		8
Audibert and associates[25]	22	F	Loud systolic murmur and thrill	+	Pain; hemoptysis; infarcts	− +	Pain; tender; enlarged; infarcts		Congenital deformity		+	+	Spleen		5
Dalous and associates[26]	22	F	Loud systolic murmur	+	Hemoptysis; physical signs; infarcts	− +	Enlarged; infarcts	+	Negative		+	+	Spleen		5
Eigen and Abel[27]	7	M	Continuous murmur; systolic thrill	+	Negative; x-ray negative	+	Enlarged	− +		+	+	+			1
Author, Case 1	13	M	Loud systolic murmur	+	Physical signs; infarcts	+	Enlarged; infarcts	+	Embolic nephritis	+	+	−	Spleen; kidneys		13

Table III. Clinical and Pathological Data in Fifteen Cases of Right-Sided Subacute Bacterial Infection Involving Chiefly the Pulmonary Valve

PATIENT	AGE	SEX	HEART	FEVER	LUNGS	BLOOD CULTURE	SPLEEN	URINE	KIDNEYS	PETECHIAE	ANEMIA	LEUCOCYTOSIS	SYSTEMIC EMBOLISM	CLUBBING	DURATION (MONTHS)
Clarke[28]	21	F	Systolic murmur; thrill	+	Pain; physical signs; infarcts										
Cautley[29]	15	F	Systolic and diastolic murmurs	+	Hemoptysis; physical signs; infarcts		Not felt; no infarcts	–	No infarcts	+			None	–	5
Bosc[30]	12	F	Loud systolic murmur	+	Physical signs			+	Congestion					+	9
Billings[31]	21	F	Systolic and diastolic murmurs	+	Physical signs; hemoptysis; infarcts	+	Enlarged; hyperplasia	–		–	+				15
Whipham[32]	11	F	Systolic and diastolic murmurs and thrill	+	Congestion	+	Enlarged; congestion	+			+			+	7
Trovor[33]	24	F	Systolic and diastolic murmurs	+	Pain; physical signs; hemoptysis; congestion; pulmonary aneurysm	+	Enlarged; congestion; no infarct				+				9
Gallavardin and associates[34]	58	M	No murmur; vegetations pulmonary valvo	+	Physical signs; infarcts?		Enlarged								1
Bishop and associates[35]	32	F	Systolic murmur and thrill	+	Cough; lobular pneumonia	–	Enlarged; congestion	+	Glomerular nephritis	+	+	–			9

In thirty-three of the cases, clinical findings referable to the *lungs* were mentioned. In twenty-seven of these (82 per cent) the findings were suggestive or diagnostic of infarction of the lungs. In thirty-six of the cases the findings in the lungs at autopsy are given; thirty of these (83 per cent) showed infarcts of the lungs. Mycotic aneurysms of the pulmonary artery were present in five of these cases.

In twenty-one instances reference was made to the clinical occurrence or absence of *embolism* of the systemic circulation; it was suspected clinically in only four patients (19 per cent). One of these had swelling of the left foot and of the lids of the left eye and gangrene of the pinnae of the ears and tip of the nose; these regions were not dissected at autopsy, but infarction of the spleen and embolic focal nephritis were found. A second patient had ptosis of the eyelid on the left and embolism was suspected, but the only indication of embolism at autopsy was an old scar in the spleen. A third patient, with enlargement and tenderness of the spleen, had sudden, severe pain in the left hypochondrium; infarction of the spleen was diagnosed clinically and confirmed at autopsy. These three patients had interventricular septal defect. The fourth patient with patent ductus arteriosus had pain in the left upper quadrant of the abdomen, which suggested infarction of the spleen; this was confirmed at autopsy. In twenty-eight cases the presence or absence at autopsy of embolism in the systemic circulation was mentioned. It was present in twelve instances (43 per cent), and ten of these patients had septal defect or patent ductus arteriosus.

Blood cultures were reported in twenty-nine instances. They were positive in eighteen cases (62 per cent) and sterile in eleven cases (38 per cent).

Enlargement of the spleen was detected in twenty-one (78 per cent) of the twenty-seven cases in which this physical finding was mentioned. In fifteen of these no infarction of the spleen was found at autopsy. At autopsy, infarction of the spleen was reported in nine cases; infarction, passive congestion, and hyperplasia, in one case; congestion and hyperplasia, in two cases; hyperplasia, in four cases; and congestion, in seven cases. In eighteen cases the appearance of the spleen at autopsy was not adequately described, although in a few of these the absence of infarcts was noted.

The *urine* was abnormal in twenty-seven cases, not abnormal in four cases, and not mentioned in ten cases. Thus, the urine was abnormal in 87 per cent of the cases in which it was mentioned. In five patients the urine was normal early in the course of the disease but became abnormal later.

The condition of the *kidneys* at autopsy was reported in twenty-three instances. In nine of these (39 per cent) glomerulonephritis was present; in three cases (13 per cent) there was embolic focal nephritis, and in a similar number infarcts were present; in four cases (17 per cent) there was congestion; and in one patient tuberculosis of the kidneys was present.

Petechiae were present in eleven cases, absent in twelve, and not mentioned in eighteen. Thus, petechiae were present in 48 per cent of the cases in which this feature was mentioned specifically. Three patients had purpura. Janeway lesions and Osler's nodes were not described in any of the cases.

TABLE IV. CLINICAL AND PATHOLOGICAL DATA IN FIVE CASES OF SUBACUTE BACTERIAL INFECTION INVOLVING CHIEFLY THE TRICUSPID VALVE

PATIENT	AGE	SEX	HEART	FEVER	LUNGS	BLOOD CULTURE	SPLEEN	URINE	KIDNEYS	PETECHIAE	ANEMIA	LEUCOCYTOSIS	SYSTEMIC EMBOLISM	CLUBBING	DURATION (MONTHS)
Moxon[39]		F	Friction rub; vegetations tricuspid	+	Infarcts		Enlarged		Granular degeneration				None		1
Luzet and Ettlinger[40]	24	F	Systolic murmur; vegetations tricuspid	+	Pain; physical signs; hemoptysis; infarcts		No infarcts	– +	No infarcts				None		4
Oerting[41]	46	M	No murmur; vegetations tricuspid; no communication	+	Pain; physical signs; x-ray; infarcts; bronchopneumonia		Not felt; infarcts	+	No infarcts	+	+	+	Spleen		1
Middleton and Burke[3]	29	M	Systolic murmur at apex; vegetations tricuspid	+	Râles	+	Enlarged	+	Palpable; glomerular nephritis		+	–	None		6
Author:—Case 5	29	F	Systolic murmur; vegetations tricuspid	+	Negative; congestion; no infarct	–	Enlarged; hyperplasia	+	Glomerular nephritis	–	+	+	None		3

Holzmann[36]	25	M	Systolic and diastolic murmurs	+	Pain; cough; physical signs; infarcts	− +	Enlarged; hyperplasia	− +	Glomerular nephritis		+	+	None		5
Brandes[37]	25	F	Pulmonary murmur; vegetations pulmonary valve and artery	+	Infarcts	− +	Congestion			+					1
Grayzel[33]	22	F	Loud systolic and diastolic murmurs	+	Infarcts	−	Enlarged	+			+	+	None		2
Dalous and associates[26]	21	F	Systolic and diastolic murmurs; systolic thrill	+	Pain; physical signs; hemoptysis; infarcts; tuberculosis	−	Enlarged; congestion	+	Congestion		+	+	None		12
Author:—Case 2.	25	M	Loud systolic murmur and thrill; no communication	+	Physical signs; x-ray; infarcts	+	Enlarged; hyperplasia; no infarcts	+	Small infarcts	−	+	+	Kidneys	+	13
Author:—Case 3.	48	M	Negative; no murmur; vegetations pulmonary valve	+	Pain; physical signs; hemoptysis; infarct; pneumonia	−	Not felt; congestion	+	Glomerular nephritis	−	+	+	None	+	6
Author:—Case 4	3	F	Systolic murmur; vegatations pulmonary valve	+	Negative; infarcts; abscesses	+	Enlarged; hyperplasia; congestion	−		−	+	+	None		2

TABLE V. SUMMARY OF CLINICAL DATA IN FORTY-ONE CASES OF SUBACUTE BACTERIAL INFECTION OF THE RIGHT SIDE OF THE HEART AND OF THE PULMONARY ARTERY; COMPARISON WITH INVOLVEMENT OF THE LEFT SIDE OF THE HEART*

	PATENT DUCTUS	SEPTUM DEFECT	PULMONARY VALVE	TRICUSPID VALVE	TOTAL RIGHT-SIDED CASES	LEFT-SIDED CASES
No. of Cases	9	12	15	5	41	
Age, years	6 to 33	4 to 29	3 to 58	24 to 46	3 to 58	4 to 74
Average	17	15	24	32	20.6	
Sex						
Male	5	7	4	2	18	males predominate
Female	4	5	11	3	23	
Murmurs	9	12	13	3	37 90%	99.2%
Pathologic murmurs	8	11	11	0	30 73%	
No murmur	0	0	2	2	4 10%	
Fever	9	11	15	5	40 100%	100 %
Infarcts, lungs						
Clinical	6	9	10	2	27 82%	57 % (systemic)
Autopsy	7	9	11	3	30 83%	
Blood culture	6	5	6	1	18 62%	78.8%
Spleen						
Clinically enlarged	2	8	9	2	21 78%	59 %
Autopsy infarct	4	5	0	1	10	
Congestion	1	2	7	0	10	
Hyperplasia	1	1	4	1	7	
Urine abnormal	7	8	8	4	27 87%	61.6%
Kidneys, autopsy						
Glomerular nephritis	2	2	3	2	9	
Embolic nephritis	2	1	0	0	3	
Infarcts	1	1	1	0	3	
Petechiae	2	5	3	1	11 48%	86.5%
Anemia	7	8	10	3	28 97%	70 %
Leucocytosis	7	5	6	2	20 87%	43.5%
Systemic Embolism Autopsy	5	5	1	1	12 43%	57 % (clinical)
Clubbing	2	2	4	0	8	46.7%
Duration, months	2 to 12	1 to 13	1 to 15	1 to 6	1 to 15	2 to 19
Average	4.4	6.8	6.9	3	5.8	5.9

*The percentages given for the right-sided cases represent the percentage of cases in which the various data are reported. Many of the reports are incomplete. The figures for the left-sided cases are aken from several sources, sometimes combined.

Clubbing of the fingers was noted in eight patients, all of whom had vegetations on the pulmonic valve. Two of these had patent ductus arteriosus and one had, in addition, interventricular septal defect. In most of the remaining thirty-three cases clubbing was not mentioned.

Anemia, as shown by pallor, by a hemoglobin level below 78 per cent, or by a red blood cell count below 4,000,000, was present in twenty-eight (97 per cent) of the twenty-nine cases in which this feature was mentioned. *Leucocytosis*, with the total white blood cell count above 10,000, was present in twenty (87 per cent) of the twenty-three cases in which the leucocyte count was given.

The *blood pressure* was recorded in twelve patients. It was not elevated in a single instance.

The estimated *duration* of the subacute bacterial infection was one to fifteen months, with an average of 5.8 months.

DISCUSSION

Subactute bacterial infection confined to the right side of the heart is mainly a disease of childhood and youth. This may be attributed to the fact that it is often a complication of congenital cardiac conditions since twenty-five of the cases (61 per cent) had congenital anomalies. Almost two-thirds of the patients with patent ductus arteriosus or interventricular septum defect were younger than twenty-one years of age.

The four cardinal diagnostic features of subacute bacterial endocarditis which were emphasized by Osler[12] and reiterated by Blumer[2] and by Libman and Friedberg[1] were present in these right-sided cases as follows: (1) evidence of a valvular lesion or of a congenital abnormality, in 73 per cent; (2) fever, in 100 per cent; (3) embolic phenomena, in 82 per cent; and (4) a positive blood culture, in 62 per cent. Information is lacking in some of the reports, but the data are adequate in a sufficient number of cases to permit the following conclusions: (1) All four of these diagnostic features were present in twelve instances (39 per cent) and at least one of these features was lacking in nineteen instances (61 per cent) of the thirty-one cases with adequate available information for this purpose; and (2) at least three of these four features were present in twenty-eight instances (82 per cent) of the thirty-four cases with sufficiently complete data for this purpose. These appear to be the most important diagnostic features when the vegetations are confined to the right side as well as when the left side is involved. Nevertheless, some of the other features of the disease may assume considerable diagnostic importance, especially when not all of the cardinal features are present.

It is important to note that the clinical manifestations of embolism were produced chiefly by infarction of the lungs[6] and that signs of systemic embolism were much less common. It is of interest, however, that systemic embolism was discovered at autopsy in two patients with vegetations confined to the right side of the heart and without any abnormal communication between the

right and left sides. In one, the vegetations were confined to the tricuspid valve and several well-defined areas of infarction were present in the spleen. In the other, the vegetations were chiefly on the pulmonic and tricuspid valves and there were multiple small infarcts in the kidneys. Both of these patients had extensive infarction of the lungs, and the possibility of thrombosis of pulmonary veins in association with infarction of the lungs is suggested as a source of the systemic emboli.

Blumgart[9] has pointed out that in cases with the infection limited to the right side of the heart, the blood cultures are commonly sterile early in the disease, although they may become positive later. Blood cultures were reported in twenty-nine of the cases in this series. They were positive in fourteen and negative in eleven, while in four they were negative one to three months after the estimated onset of the disease and positive later in its course. The fourteen initially positive cultures were obtained from ten days to fourteen months after the estimated onset of the disease. In the eleven patients who yielded no growth the cultures were obtained from one to eight months after the estimated onset of the disease. Thus, it appears that not only is there a delay in some cases in yielding positive cultures, but many patients have sterile cultures throughout the course of the disease. As a result, one of the cardinal diagnostic features of the disease is lacking in approximately one-half of those patients examined early in the course of the disease.

Differential diagnosis may be difficult when the blood cultures are sterile. For example, a youth of 21 years had a systolic murmur at the apex of the heart, fever, anemia, leucocytosis, and pronounced enlargement of the spleen; he was thought at first to have the abdominal type of Hodgkin's disease, but the subsequent appearance of petechiae and positive blood cultures led to the diagnosis of the splenomegalic form of subacute bacterial endocarditis. In the presence of a cardiac murmur, conditions characterized by pulmonary lesions and fever may resemble right-sided subacute bacterial endocarditis in many respects, especially if the spleen is enlarged and if anemia and leucocytosis are present. For example, a 40-year-old woman had repeated infarction of the lungs, persistent low-grade fever, leucocytosis, and a systolic murmur over the precordium, and, although repeated blood cultures were sterile, the diagnosis of right-sided subacute bacterial endocarditis was entertained. Later, however, the presence of phlebothrombosis in the lower extremities became apparent, and treatment for this condition was followed by complete recovery.

The four cardinal diagnostic features, when present, will point most surely to the presence of subacute bacterial endocarditis. Nevertheless, some of these features may be lacking in cases with right-sided involvement, especially early in the course of the infection when the blood cultures are so commonly sterile. For this reason, greater diagnostic significance may be attached to the other features of the disease, such as enlargement of the spleen, petechiae, anemia, leucocytosis, and evidence of renal involvement.

The presence of vegetations in both the right and left sides of the heart is fairly common. This study has revealed no criteria by means of which it

can be ascertained clinically that the infection is confined to either the right side or the left side, but pulmonary embolism suggests vegetations on the right side whether or not the left side is involved.

SUMMARY

In less than 4 per cent of patients with subacute bacterial endocarditis, the vegetations are confined to the right side of the heart. In patients with patent ductus arteriosus with subacute bacterial endarteritis the infection may be confined to the ductus and the pulmonary artery.

A study of thirty-six such cases reported in the literature and five newly reported cases forms the basis for a description of the clinical features of subacute bacterial infection confined to the right side of the heart and the pulmonary artery.

The four cardinal diagnostic features of left-sided subacute bacterial endocarditis are of chief importance in the diagnosis of the right-sided type as well, but because the blood cultures are often sterile and embolism is sometimes absent or obscure, greater diagnostic significance may be attached to the other features of the disease.

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THE EFFECT OF SYMPATHETIC STIMULATION ON AURICULAR FLUTTER

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FEW studies dealing with the effect of sympathetic stimulation on auricular flutter are available. This fact contrasts sharply with the numerous careful investigations concerning the action of stimulation of the vagus nerves, which leads to the well-known paradoxic increase of rate.

The duration of postfaradic fibrillation in dogs was found to be shortened by sympathetic stimulation.[16] The problem was again studied on the dog after the administration of physostigmine or muscarine.[11] Naturally, the results were modified by the fact that these substances have some direct action on the heart muscle. In these experiments, auricular flutter and auricular fibrillation caused by faradization disappeared faster during sympathetic stimulation. The rate of auricular flutter was increased "within narrow limits" when one of the sympathetic nerves was stimulated with a faradic current. Thus, it rose in one experiment from 556 to 569, and in another from 443 to 450; the greatest change was found in a third experiment, where it rose from 460 to 522 during stimulation with a strong faradic current. The stimulation of the left accelerator nerves produced a greater effect than that of the right ones. Postfaradic auricular flutter and fibrillation, however, are not stationary phenomena, for there is from the beginning a tendency toward slowing of the rate and reappearance of sinus rhythm. Occasionally the flutter ended just as these authors[11] began stimulation of the sympathetic nerves.

In previous publications it has been shown[13] that the injection of 0.05 c.c. of a 0.05 per cent solution of aconitine leads to auricular flutter or fibrillation. These arrhythmias persist for more than sixty minutes. An added advantage of this method is the focal action of aconitine; only the area of the heart into which the injection is made is affected, the rest of the muscle remaining practically uninfluenced. The present communication deals with a study of the effect of faradic stimulation of the sympathetic nerves during auricular flutter caused by the topical application of aconitine.

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METHOD

The hearts of dogs weighing between 5.0 and 12 kilograms were exposed, during Nembutal anesthesia and artificial respiration, by resection of the sternum and parts of the adjacent ribs. In the majority of the experiments the right vagus nerve was divided in the neck. The sympathetic chain was severed at the level of the pulmonary hilus and the cardiac branches of the sympathetic nerves were cautiously dissected. These nerves were placed on a shielded electrode and stimulated for ten to fifteen seconds with a strong faradic current from a Cambridge inductorium. The pericardium was opened and 0.05 c.c. of the 0.05 per cent aconitine solution was injected into the area of the sinus node, subepicardially, or into the wall of the right or left auricular appendix. In other experiments the surface of the right or left auricular appendix was abraded with the point of a needle over an area about 2.0 mm. in diameter, and a minute quantity of the aconitine solution was applied at this point. Within one minute auricular flutter appeared. The different modes of application had no discernible influence on the results. In all experiments, as soon as the tachycardia appeared, the diagnosis of auricular flutter was established by faradic stimulation of the right vagus nerve in the neck, which led immediately to the paradoxic increase of auricular rate. All electrocardiograms were taken on Lead II.

RESULTS

Sympathetic Stimulation Without Atropinization.—In all experiments the flutter rate increased during and shortly after the stimulation of the right as well as of the left sympathetic cardiac nerves. Often the increase was spectacular. Repeatedly, auricular fibrillation appeared upon sympathetic stimulation; this changed again into flutter either spontaneously or after cooling of the area to which aconitine had been applied. In most experiments the procedure was repeated, with the same results.

Fig. 1 was obtained in the experiment of May 6, 1947. Following the application of aconitine, auricular flutter appeared, with a rate of 214 (Fig. 1,*A*). Faradic stimulation of the right sympathetic cardiac nerves increased the auricular rate to 500 (Fig. 1,*A*). Fifteen minutes later the auricular rate had returned to 214 (Fig. 1,*B*). Stimulation of the left sympathetic cardiac nerves increased the auricular rate to 428; the ventricular rate was 214, as the result of a 2:1 A-V block. Eight minutes later the auricular rate was 285 (Fig. 1,*C*). The left sympathetic nerves were again stimulated, and auricular fibrillation appeared for two minutes and thirty seconds.

In the experiment of April 8, 1947, auricular flutter existed with an auricular rate of 375 and a 2:1 A-V block. Stimulation of the right vagus nerve in the neck caused an increased A-V block, and the auricular rate rose to 428 (Fig. 2,*A*). Stimulation of the right sympathetic cardiac nerves caused auricular fibrillation (Fig. 2,*B*). Cooling of the area on which the aconitine had

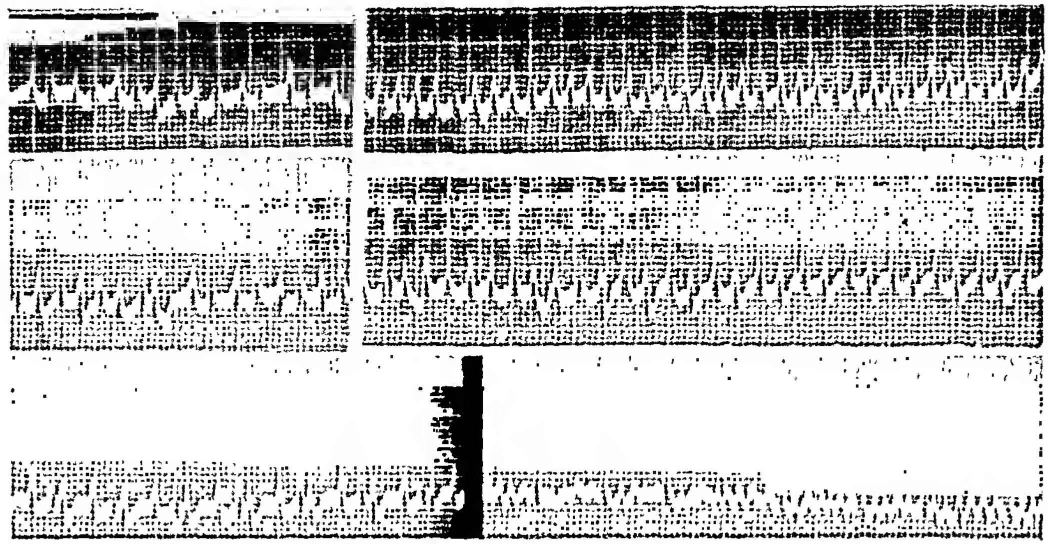
A.
B.
C.


Fig. 1.—*A* shows the electrocardiogram before and after stimulation of the right sympathetic cardiac nerves, *B* and *C*, before and after the stimulation of the left sympathetic cardiac nerves.

been injected stopped the fibrillation immediately (Fig. 2,*C*) and sinus rhythm reappeared. Interruption of the cooling led to the immediate appearance of auricular flutter with a rate of 336 (Fig. 2,*C*). Short faradic stimulation of the right vagus nerve converted the flutter into fibrillation without any latent period (Fig. 2,*D*).

In the experiment of April 29, 1947, regular auricular flutter with a rate of 300 and a 2:1 A-V block existed (Fig. 3,*A*). Faradic stimulation of the left sympathetic cardiac branches increased the flutter rate to 330, and suddenly auricular fibrillation appeared (Fig. 3,*A*). Approximately two minutes later the fibrillation changed spontaneously into auricular flutter (Fig. 3,*B*). The right cardiac sympathetic nerves were stimulated about seven minutes later, when flutter still prevailed, with a rate of 333. Again transitory auricular fibrillation appeared (Fig. 3,*C*).

Table I shows the result of the stimulation of the right or left sympathetic nerves in thirteen dogs during auricular flutter. In a few experiments the increase of rate was slight. In others it amounted to more than 100 beats per minute, and in eleven experiments auricular fibrillation appeared upon sympathetic stimulation. Usually this was a temporary phenomenon, but renewal of the sympathetic stimulation again caused fibrillation. There was no evidence that the duration of flutter was shortened by faradic sympathetic stimulation. All the changes just mentioned appeared with the usual latency after the beginning of the stimulation, namely, after about six to ten seconds, and the increase of the flutter rate lasted for about one-half minute after the end of the stimulation. A difference in the effectiveness of the stimulation of the right sympathetic cardiac nerves as compared with the left was not evident.

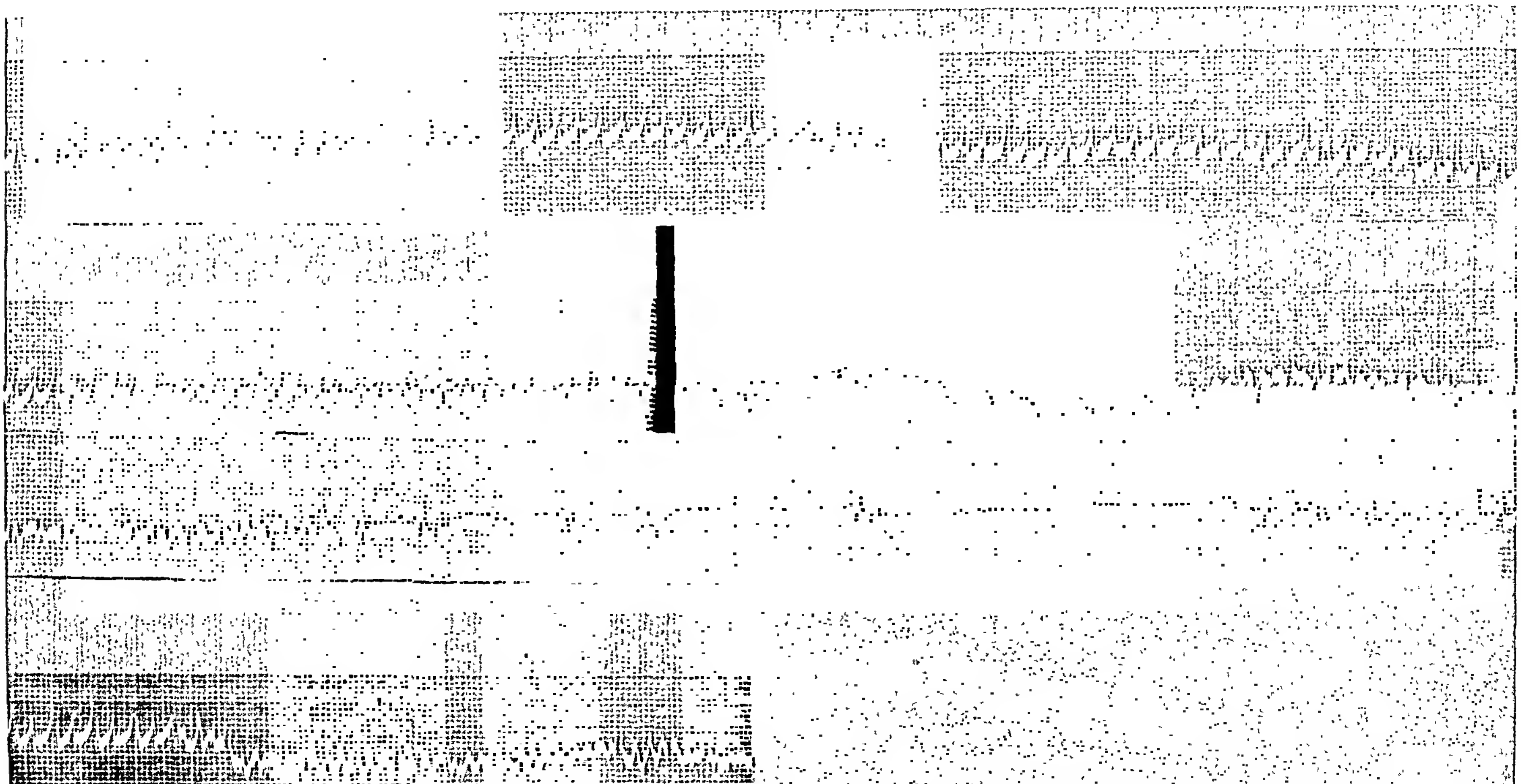


Fig. 2.—*A* shows the effect of faradic stimulation of the vagus during auricular flutter; *B* was taken before and after stimulation of the right sympathetic cardiac nerves. *C* shows the effect of cooling of the area of application of aconitine. *D* was recorded during a second faradic stimulation of the right vagus.

TABLE I. THE EFFECTS OF STIMULATION OF THE RIGHT OR LEFT SYMPATHETIC NERVES IN THIRTEEN DOGS DURING AURICULAR FLUTTER

DATE	SIDE STIMULATED	RATE BEFORE	RATE IMMEDIATELY AFTER	RATE 2 MINUTES AFTER	REMARKS
4/ 1/47	Right	420	480	420	Stimulation of right twice caused fibrillation; stimulation of left caused fibrillation three times
4/ 8/47	Right	375	428		Fibrillation
	Right	352	374	352	
4/22/47	Right	316			Fibrillation
4/29/47	Right	352	428	250	
	Left	272			Fibrillation
	Right	333			Fibrillation
	Left	333			Fibrillation
	Left	333			Fibrillation
	Left	300			Fibrillation
5/ 6/47	Right	214	500	214	
	Left	214	428	214	
	Left	285			Fibrillation
5/13/47	Right	300			Fibrillation
5/20/47	Left	214			Fibrillation
	Left	374			Fibrillation
5/27/47	Left	300			Fibrillation
6/ 3/47	Right	428			Fibrillation
9/16/47	Right	214	250	250	
	Right	214	250	214	
	Right	214	250	214	
9/23/47	Right	300	374	300	
	Right	333	428	333	
	Right	300	374	300	
	Right	300			Fibrillation
	Right	300			Fibrillation
10/ 7/47	Right	214	250	214	
	Right	286			Fibrillation
	Right	222	333	222	
10/14/47	Right	230	300	230	

Sympathetic Stimulation After Atropinization.—The latent period after sympathetic stimulation which has been referred to demonstrates that simultaneous stimulation of vagus fibers is not responsible for the changes just described. The effect of the stimulation of the vagus nerve was always recorded immediately; the increase of rate disappeared with the end of the stimulation.

In order to eliminate any possibility of simultaneous stimulation of vagus fibers on faradization of the sympathetic nerves, the experiments were repeated

A.

B.

C.

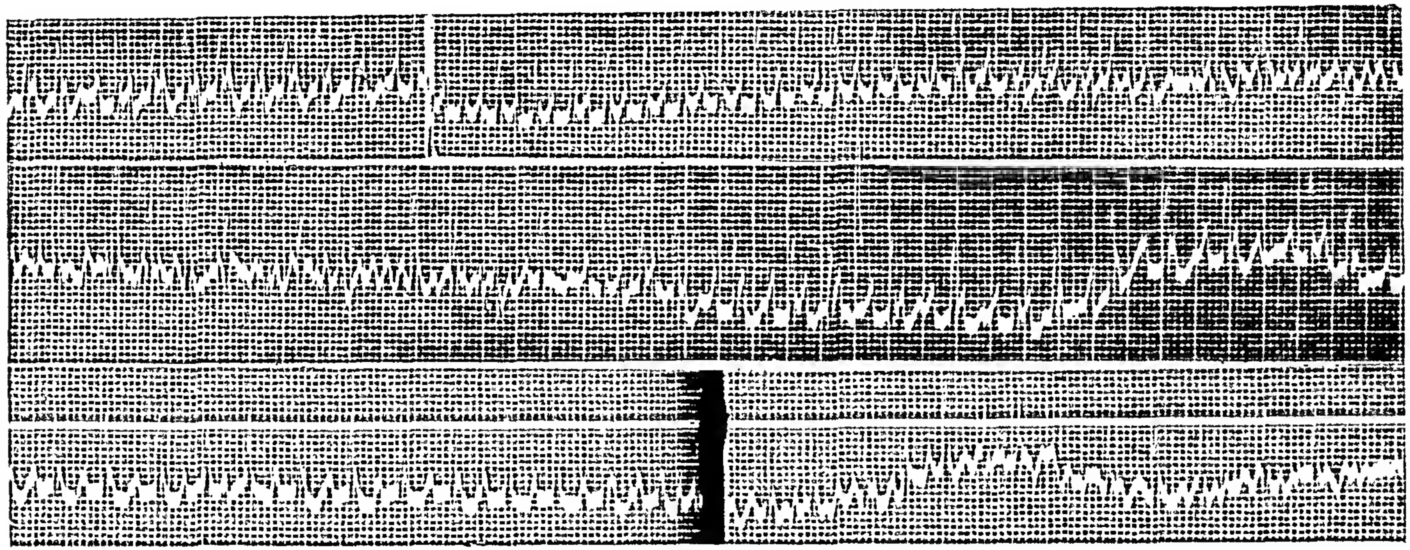


Fig. 3.—*A* was obtained before and immediately after stimulation of the left sympathetic cardiac nerves. *B* was registered two minutes later. *C* was obtained before and immediately after the faradic stimulation of the right sympathetic cardiac nerves.

Fig. 4.

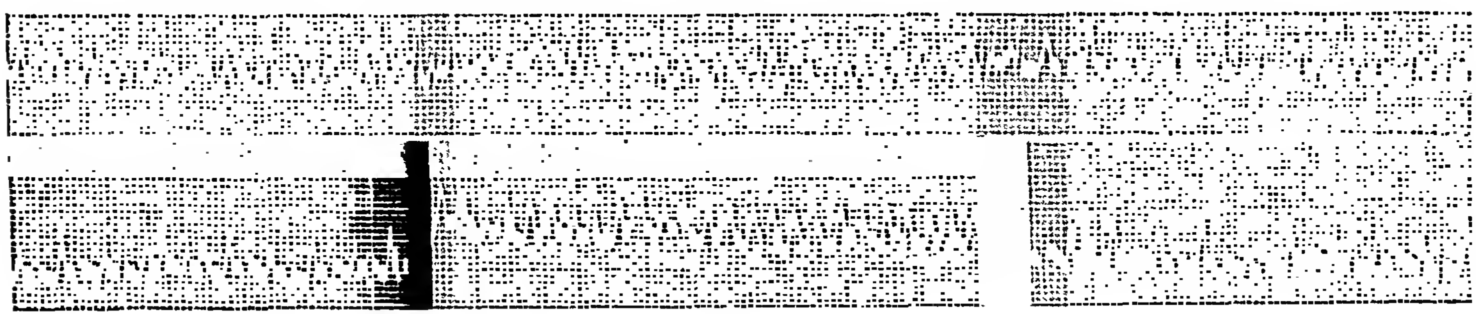


Fig. 5.

Fig. 4.—Transition from auricular fibrillation into flutter after intravenous injection of atropine.

Fig. 5.—After atropinization; the three strips show the electrocardiogram before stimulation of the right sympathetic nerves, immediately thereafter, and about two minutes later.

after the intravenous injection of 1.5 to 2.0 c.c. of atropine sulfate in a 1:1,000 solution. This injection invariably caused a change in the existing rate or rhythm. In eight experiments in which auricular fibrillation existed at the time of the injection, in every instance it was replaced by auricular flutter within a few seconds after the injection.

Fig. 4 was obtained in the experiment of Jan. 27, 1948. Auricular fibrillation was present (beginning of tracing), and the transition into auricular flutter with a rate of 285, nine seconds after the end of the injection, is clearly visible. If auricular flutter prevailed at the time the atropine was administered, the rate fell slightly but no other changes were observed. In order to rule out the presence of a sinus tachycardia after atropinization, the application of aconitine was always repeated.

Table II shows that after atropinization, faradization of the sympathetic nerves still causes an acceleration of the auricular rate, but not so regularly, and usually the acceleration is of a much lesser degree than before atropine administration. Auricular fibrillation was never observed after atropinization, and in four experiments the rate was not influenced at all despite the use of strong faradic currents.

In one experiment only was a pronounced acceleration of rate observed. On this occasion (Dec. 9, 1947), the auricular flutter rate after atropine was 240 (Fig. 5). After stimulation of the right sympathetic cardiac nerves the auricular rate increased to 420 beats per minute and then fell again to 240 (Fig. 5, third strip).

The usual result after atropinization was like that shown in Fig. 6, which was obtained in the experiment of Nov. 25, 1947. The auricular rate was 250 (first part of Fig. 6). The stimulation of the right sympathetic nerves for ten seconds led to no increase of rate (second part of Fig. 6), but marked and typical changes of the RS-T segment and the T waves show that the sympathetic stimulation had a pronounced effect on the myocardium.

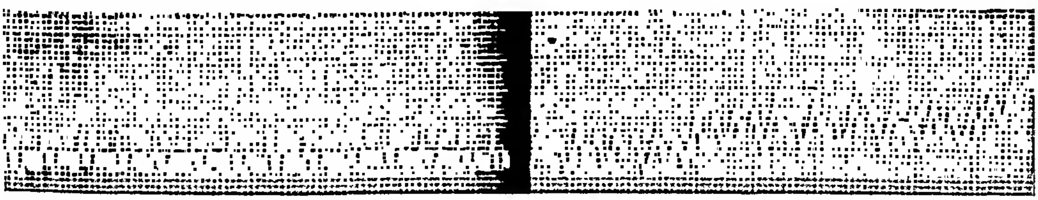


Fig. 6.—After atropinization stimulation of the right sympathetic cardiac nerves causes marked changes of the RS-T segments without a change of rate.

Fig. 7 shows strips from tracings obtained on Jan. 27, 1948. In this experiment the P waves were unusually high. The auricular rate after the application of aconitine and administration of atropine was 260 (Fig. 7,*A*). Stimulation of the right cardiac sympathetic nerves caused a change of the form of the T waves (Fig. 7,*B*), but the cardiac rate was only 272. Three minutes later the electrocardiogram (Fig. 7,*C*) was again like that shown in Fig. 7,*A*. The intravenous injection of epinephrine, 1.5 c.c. of a 1:100,000 solution, caused

TABLE II. THE EFFECTS OF STIMULATION OF SYMPATHETIC NERVES AND OF EPINEPHRINE UPON THE AURICULAR RATE, BEFORE AND AFTER ADMINISTRATION OF ATROPINE

DATE	SIDE STIMULATED	BEFORE ATROPINE		AFTER ATROPINE		BEFORE EPINEPHRINE	AFTER EPINEPHRINE
		BEFORE STIMULATION	AFTER STIMULATION	BEFORE STIMULATION	AFTER STIMULATION		
11/11	Right	330	428				
	Right			250	250		
	Right			250	250		
	Right			250	250		
11/25	Right	352	Fibrillation*				
	Right			250	250		
	Left			272	300		
12/ 2	Right			250	300		
	Right			250	270		
	Right			270	270		
12/ 9	Right	250	330				
	Right			240	420	250	300
12/16	Right			230	250		
12/23	Right			250	300	230	270
	Right			270	300		
1/ 6	Right			230	230	214	250
1/13	Right			230	300		
	Right			300	300		
1/20	Right	270		250			
	Right	270		250			
1/27	Right		Fibrillation*		250		
	Right		Fibrillation*		250		
	Right			260	272	260	260
	Right			270	285		
	Left			270	270		
	Left			250	250		
	Right			250	250		
	Left			250	250		
2/ 3	Right			300	352	230	250
	Right			285	330		
	Left			280	330		
2/10	Right			230	252		
	Right			230	252	250	250
	Right			252	252		
	Right			214	252		
2/24	Right			250	300	250	300
	Right			272	300		
	Right			250	272		
4/ 6	Right			240	240		
	Right			240	240		
	Right			240	240		
	Right			250	250		
	Right			250	250		
	Right			250	250		

*Sympathetic stimulation was never observed to produce fibrillation after atropinization.

changes of the T waves similar to those occurring after sympathetic stimulation but no increase of the rate, which remained at 260 (Fig. 7, *D*).

The injection of 1.5 to 2.0 c.c. of the epinephrine solution was repeated in six experiments, always after atropinization, and elicited the same responses with regard to the auricular rate as the stimulation of the sympathetic nerves.

The appearance of the pronounced changes of the RS-T segments and T waves, as well as the clearly visible augmentation of auricular and ventricular contractility following sympathetic stimulation or an injection of epinephrine, testifies that the cardiac sympathetic nervous system remained active and responded in the usual way throughout the experiments. Therefore the frequent absence of an increase in rate is significant.

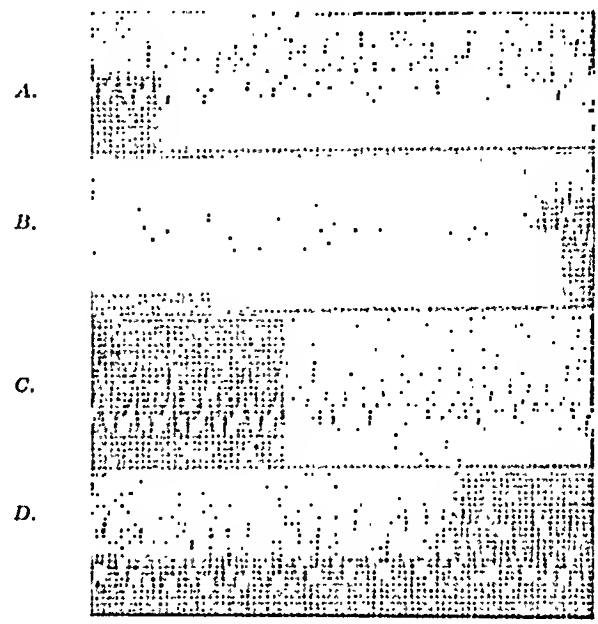


Fig. 7.—*A* was taken before, and *B*, immediately after stimulation of the right sympathetic nerves (after atropinization). *C* was obtained three minutes later. *D* was taken after the injection of adrenalin.

DISCUSSION

Against the classification of the auricular tachycardias in these experiments as auricular flutter, two arguments may be brought forward. First, the auricular rate in some experiments was as low as 214. There is no doubt, however, that such flutter rates do occur in the dog, and some of the classic experiments of Lewis were performed during auricular flutter with equally low rates. Second, a characteristic of auricular flutter, absent in these tracings, is the continuity of the flutter waves. It must be recognized, however, that in the experimental animal as well as in man a definite zero line often occurs between the individual auricular deflections. The response of these tachycardias to vagus stimulation with an increase of rate speaks, according to our present knowledge, for the presence of flutter. This diagnosis is also suggested by the frequent change of this tachycardia into auricular fibrillation by various measures (Figs. 1, 2, and 3).

The experiments show clearly an acceleration of auricular rate during and immediately after faradic stimulation of the sympathetic nerves leading to the heart. This acceleration was sometimes pronounced, causing the appearance of transitory auricular fibrillation.

In each of eight experiments an intravenous injection of atropine during auricular fibrillation induced the emergence of auricular flutter.

Faradic stimulation of the right or left sympathetic cardiac nerves after atropinization did not cause a marked acceleration of rate except on a few occasions. Usually the rate was but slightly increased, or unchanged, although the typical alterations of the RS-T segment and of the T waves appeared. Auricular fibrillation was not observed when the sympathetic nerves were stimulated after atropinization.

Injections of epinephrine evoked the same general effects as sympathetic stimulation. Moderate acceleration, often interrupted by bouts of paroxysmal ventricular tachycardia, was seen after atropinization, but occasionally the rate remained unchanged despite marked changes of the T waves.

The transformation of auricular fibrillation into flutter by atropine could be attributed to the effect of the latter on the refractory phase. Atropine prevents the postfaradization fibrillation[16] and terminates this type of fibrillation, if present.[6,16] It has been claimed that atropine does not inhibit auricular fibrillation caused by chemical substances.[16] Following the administration of 2.0 mg. of atropine subcutaneously a slight fall of auricular rate has been registered in some but not in all patients with auricular flutter.[14]

The prolongation of the refractory phase after atropinization is the most probable cause for the effect of atropine on auricular fibrillation. It is possible that the normal tonus of the cholinergic nerves helps in maintaining auricular fibrillation following application of aconitine. The diminished effect of sympathetic stimulation after atropinization is certainly not due to the absence of sympathetic effects on the heart. It is possible, however, that in auricular flutter the direct action of sympathetic stimulation on the auricular rate is actually always a minor one and that the more pronounced results seen before atropinization are due to indirect vagal effects. Thus, the increase of blood pressure may lead to a reflex increase of the tonus of the vagus nerves and so induce acceleration of the flutter. These reactions would be abolished by the administration of atropine.

It seems established that the chief physiologic effect of sympathetic stimulation on the heart consists in a shortening of systole and of the refractory period. This was found in dogs both during sympathetic stimulation[15] and by injection of epinephrine.[1,10,15] In three out of four experiments the refractory phase of the specific tissue from the dog's ventricle was shortened during the action of epinephrine.[2] The duration of the systole as measured in the electrocardiogram was shortened in man after exercise and after epinephrine.[4,8] In one case of auricular flutter in man the flutter rate increased on exertion.[9] The shortening of systole following sympathetic stimulation or epinephrine seems to be independent of mechanical efficiency and cardiac rate. A prolongation of the re-

fractory phase upon sympathetic stimulation has been reported only in the frog heart.[3,5,7]

Those who accept the circus movement theory for the explanation of auricular flutter can explain the increase of the flutter rate during sympathetic stimulation by the shortening of the refractory phase. This, like the stimulation of vagus nerves, causes the disappearance of barriers, in the form of islands of refractory tissue, to the central wave, and thus leads to its faster circulation. It has been shown, however, that the flutter and the fibrillation in our experiments could readily be stopped by cooling the area on which the aconitine was applied (Fig. 2). Removal of the cooling thermode made the auricular fibrillation or flutter reappear immediately.[13] This result cannot be explained if one assumes the presence of a circus movement. Therefore, an increase of rate of the stimulus formation in a single center, as a result of the shortening of the refractory phase during sympathetic stimulation, must be considered.

SUMMARY

Faradic stimulation of the right or left sympathetic nerves of the heart of the dog in situ leads to a distinct and often marked acceleration of auricular flutter caused by topical application of aconitine. Flutter is often transformed into fibrillation by this measure.

Administration of atropine regularly changes auricular fibrillation into flutter or slows the rate of auricular flutter.

Faradic stimulation of the sympathetic nerves or the injection of epinephrine, after atropinization, causes only a slight acceleration of the existing flutter rate; occasionally these measures remain without effect on the auricular rate despite the appearance of marked and typical changes of the RS-T segments.

It is concluded that the more marked effect of sympathetic stimulation before atropinization is due to reflex increase in vagus tonus.

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ATRIAL FIBRILLATION INDUCED BY EPINEPHRINE IN HYPOTHERMIC DOGS

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ATRIAL fibrillation occurs in association with a wide variety of clinical conditions and frequently without other evidence of cardiac disturbance.[1-5] It is well known that the vagus nerves can influence the character and duration of atrial fibrillation and that concurrent vagus stimulation facilitates induction of fibrillation, as, for example, in direct electrical stimulation of the auricles.[6,7] Vagomimetic and vagus-potentiating drugs such as pilocarpine and physostigmine act similarly.[8] Supposedly, vagus stimulation facilitates fibrillation by shortening the refractory period of atrial muscle, thus permitting re-entrant excitation.[9]

Several writers have reported atrial fibrillation following vagal stimulation alone in hearts under various abnormal conditions.[10,11,12] No drugs injected intravenously produce atrial fibrillation consistently, but the most effective are the vagomimetic and vagus-potentiating drugs, acetylcholine,[13,14] Mecholyl,[15] and physostigmine.[16] Direct application of Mecholyl to the atrium, together with mechanical stimulation, is a reliable means of initiating fibrillation.[17] Further, the drugs most effective in preventing atrial fibrillation, in slowing fibrillation, or in restoring normal rhythm are vagolytic agents, such as atropine,[8] quinidine,[1,18] and atabrine.[19] It is probable that vagus activity is involved in inciting the atrial fibrillation which has long been recognized as a common complication of thyrotoxicosis[20] and rheumatic fever.[21] Moreover, vagus activity may obviously be suspected in many other states commonly leading to fibrillation, such as vomiting, gastrointestinal disturbances, hypertension, and exertion,[4] and in fibrillation associated with myocardial infarction.[22] In no such conditions can vagal activity be ruled out definitely as a contributing cause, and in many the occurrence of fibrillation is associated with a prolonged P-R interval.[22] Nevertheless, it seems clear that in most cases increased vagal activity is not the only factor involved since even strong stimulation of the vagi in experimental animals rarely causes fibrillation, and may even stop established fibrillation.[7,8,23,24]

Demonstration that atrial fibrillation could be started readily by intravenous administration of Mecholyl in thyrotoxic patients led Nahum and Hoff[20] to postulate that fibrillation results from simultaneous action of vagus inhibition and an excitatory "E" factor (in this case, thyroid hormone) on the heart.

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The cardiac sympathetic nerves and epinephrine clearly constitute possible "E" factors, but previous studies have suggested that the cardiac sympathetic nerves and sympathomimetic drugs are of minor importance in atrial fibrillation. Winterberg[6] reported that sympathetic stimulation tended to decrease the duration of fibrillation induced by direct faradization of the atria, possibly by counteracting vagus tone, but he later noted[25] that combined stimulation of the cardiac accelerator and vagus nerves in curarized dogs sometimes caused atrial fibrillation which was soon followed by ventricular fibrillation. There are a few reports of atrial fibrillation started by epinephrine injections, but in most of these it is not possible to determine what accessory factors may have been involved. Smith and Moody[26] reported epinephrine-incited fibrillation in two patients who had exhibited either atrial fibrillation or frequent extrasystoles on forced breathing. Otto[27] stated that intravenous injection of very small doses of epinephrine "frequently" starts fibrillation in elderly normal persons. Atropine prevents this response, so that vagus involvement is indicated. Cowan and Ritchie[28] listed epinephrine as one of many agents which may induce atrial fibrillation in intact animals and in perfused hearts. Hume[29] cited a single doubtful case of fibrillation started by epinephrine. Rosenblum, Hahn, and Levine[30] found that thyroxine treatment greatly sensitized the hearts of rabbits and dogs to epinephrine and they obtained atrial fibrillation with epinephrine in five of twenty rabbits that had been treated with thyroid, with doses which did not disturb the cardiac rhythm in normal animals. Petzetakis[31] produced atrial fibrillation in rabbits with lethal doses of epinephrine.

In none of these cases was the mechanism of action of the drug studied, and reflex vagus activation obviously might have been involved in many of them.

A possible exception to the rule of vagus involvement in inciting atrial fibrillation is the fibrillation that occurs in hypothermia in man. All observers agree that atrial fibrillation is commonly seen in severe hypothermia in man,[32-35] but such experimental studies as have been made[36] indicate that the bradycardia, delayed conduction, and other cardiac changes found in hypothermia in animals are due to the direct action of cold on the heart and that there is no vagal overactivity.

This study was begun in an attempt to determine the causes of atrial fibrillation in hypothermia. In this we have failed since it proved impossible to cause spontaneous atrial fibrillation in dogs by cooling. Twenty-eight dogs and four cats were cooled to body temperatures as low as 13°C. in some cases, but in none did atrial fibrillation occur as a result of hypothermia alone. This experience agrees with that of others.[36,37] Although changes in the electrocardiogram indicative of profound disturbances in atrial conduction and excitation were found, these changes did not lead to fibrillation or flutter. At present it appears that atrial fibrillation in hypothermia is a human idiosyncrasy.

Since hypothermia alone did not cause fibrillation, we attempted to produce it by accentuation of some possible predisposing conditions. Three procedures were used: (a) vagus nerve stimulation; (b) intravenous injection of epinephrine; and (c) epinephrine injections followed by vagal stimulation. These procedures were applied to anesthetized animals at normal body temperatures and to animals

subjected to various degrees of cooling. In dogs, atrial fibrillation was produced by all three procedures, but with none was the phenomenon regularly repeatable even in successive trials on the same animal, and there appeared to be no consistent relation between the degree of hypothermia and the ease with which fibrillation could be induced. Attempts to initiate fibrillation in the cats, either by vagus stimulation or by epinephrine injection, were unsuccessful. The results demonstrate clearly the synergic effects of vagus overactivity and excitant factors in the production of atrial fibrillation, and are presented in that context.

METHODS

Twelve of the twenty-eight dogs used in the experiments were anesthetized with sodium pentobarbital (Nembutal) and one dog was decerebrated under ether. The remaining dogs were anesthetized with sodium ethyl (1-methylbutyl) thiobarbiturate (Pentothal), which was discontinued at the onset of cold narcosis. Usually no further anesthetic was needed after the rectal temperature reached 33° centigrade. No differences attributable to anesthesia were noted with respect to atrial fibrillation, but ventricular fibrillation occurred more commonly in cooled animals anesthetized with sodium pentobarbital. Thiobarbiturate caused frequent ventricular extrasystoles in some animals with high arterial pressures[38] at near-normal rectal temperatures. Since progressive respiratory failure began when rectal temperatures reached about 23°C., and since anoxia is known to predispose to fibrillation,[39] artificial respiration was given either from the start or before anoxic symptoms appeared. Arterial pressure was recorded continuously by femoral cannulation. Electrocardiograms were taken usually with Lead II and the electrical behavior of the heart was followed continuously by means of a cardioscope. The vagus nerves were exposed for cooling or stimulation in many of the experiments, but were usually left intact. Stimulation was induced by induction coil currents. Before cooling was begun, the stimulus strengths needed to cause slight slowing and complete sinus arrest were determined for each vagus nerve and these strengths used as standards throughout the experiment. When the left vagus nerve failed to cause arrest, the strength needed to cause arrest with the right was used for the left also. In cats arrest was rarely possible with stimulation of either vagus nerve, and so an arbitrary strong stimulus was used.

For reversible block of the vagi by cooling, metal clips about 1.0 cm. long were placed around the intact nerves at the start of the experiment. Water or brine at the desired temperature was circulated through copper pipes soldered to the clips.

Epinephrine was given intravenously, either by injection in 1:1,000 or greater dilution, or by slow intravenous drip of dilute solution (see Results). Cooling of the animal was effected by packing the animal in ice, the chest being left free from ice to avoid direct cooling of the heart. The chest was opened late in some experiments for direct observation of the heart and for the application of epinephrine directly to the auricles.

RESULTS

Effect of Vagus Stimulation.—Frequent attempts were made to start atrial fibrillation by strong stimulation of the intact vagi in fifteen dogs and two cats. In six of the dogs fibrillation occurred at least once and outlasted the period of stimulation. In one dog three out of ten stimulations of the right vagus and two out of ten stimulations of the left vagus were effective. Stimulation of the left vagus produced fibrillation only in this one dog after marked sinus slowing. In one dog with the vagi sectioned, stimulation of the peripheral right vagus induced fibrillation. The data are inadequate for statistical evaluation. Although atrial fibrillation resulted from twelve out of ninety-one right vagus and two out of eighty-six left vagus nerve stimulations, there was no clear relation between body temperature and this effect of vagus stimulation since fibrillation was produced at rectal temperatures varying from 37.6° to 27.6° centigrade. One animal fibrillated at 37.6° and 28.3°C. but not at intermediate or lower temperatures. The relative effectiveness of the two vagi is in agreement with the results of Jourdan and Froment,[12] who obtained atrial fibrillation in six out of twenty-one chloralosed dogs (presumably kept at normal body temperature) by prolonged right vagus stimulation and in one of twenty by left vagus stimulation. Grosse-Brockhoff and Schoedel[40] suggested that the heart is more sensitive to vagal action during hypothermia although there is no accentuation of vagus activity. We have found no evidence of increased sensitivity but rather of decreased sensitivity to direct electrical stimulation of the vagi; the stimulus strengths needed to cause sinus bradycardia and arrest remained unchanged by cooling or became substantially increased.

Fibrillation never began at the start of the stimulation period, and usually only after several "escape" beats had occurred. In many cases fibrillation began immediately following a ventricular beat, suggesting an A-V nodal origin, but one electrocardiogram was obtained (Fig. 1,*C*) which showed fibrillation beginning 1.6 seconds after the preceding beat and 0.3 second before the succeeding ventricular beat. This finding indicated an ectopic auricular origin. The relative ineffectiveness of the left vagus in inducing fibrillation is presumably due to the usual paucity of sinus node and atrial innervation by this nerve in the dog.

Effects of Epinephrine.—Epinephrine was administered intravenously during progressive hypothermia to fifteen dogs and one cat. Three of the dogs died in ventricular fibrillation following the first or second injection. Two dogs given epinephrine by slow intravenous drip at a rate of 1.0 to 4.0 micrograms per kilogram per minute for periods up to forty minutes did not fibrillate although arterial pressure was much increased. The failure to produce fibrillation with this method may be due to the low concentrations of adrenaline, but two other dogs each received two large injections of 0.05 to 0.1 mg. without showing fibrillation. The remaining eight were given repeated injections of 0.01 to 0.05 mg. per kilogram with ratios of "successes" to number of injections of 6:7, 4:7, 4:6, 1:7, 0:1, 0:3, 0:3, and 0:5 (Fig. 1,*A* and *B*).

The high incidence of fibrillation compared with that reported in previous studies suggests that hypothermia was a contributing cause, but no clear relation to rectal temperature is evident in the data. Fibrillation was induced by epinephrine at rectal temperatures from 37° to 25.0° centigrade. The lack of previous reports may be due in part to the difficulty involved in detecting transient atrial fibrillation by indirect means in the presence of ventricular tachycardia and extrasystoles induced by large doses of epinephrine. Cold reduces this difficulty considerably.

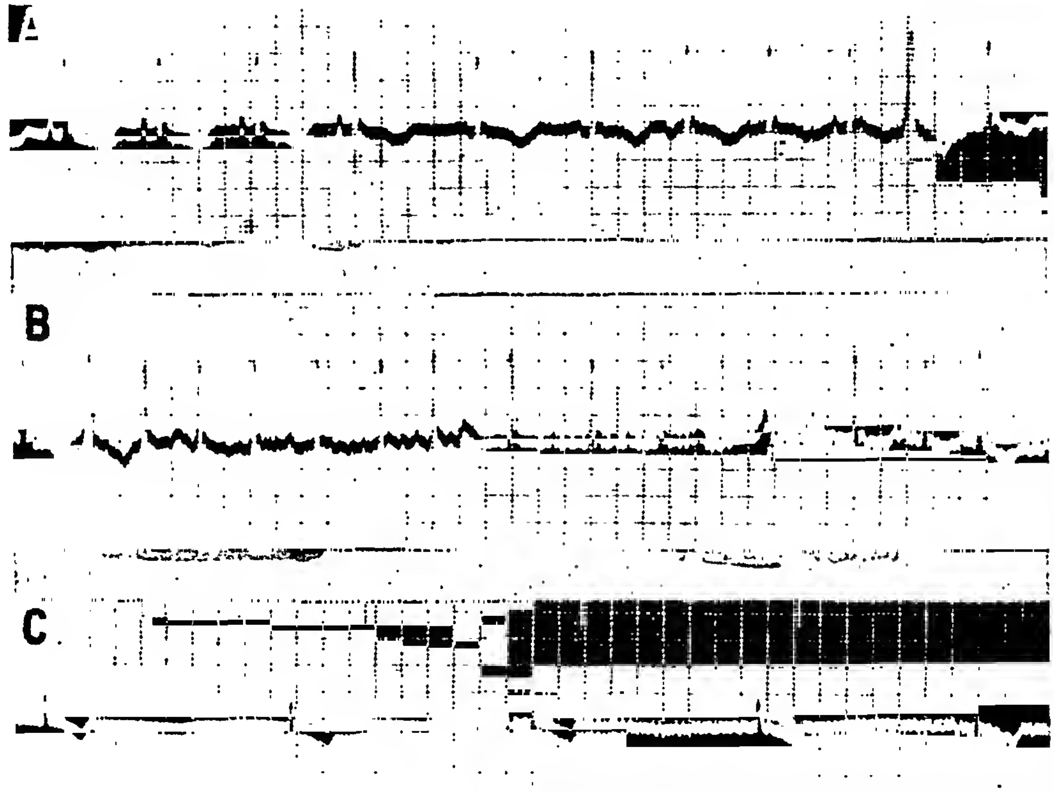

Fig. 1.—*A* and *B*, Continuous record. Development of atrial fibrillation after intravenous injection of epinephrine. *C*, Development of atrial fibrillation after right vagus stimulation. The square white signal marks the cessation of stimulation.

Integrity of the vagus nerves is probably necessary for atrial fibrillation following epinephrine. In two animals which had each fibrillated twice in succession following epinephrine, both vagi were blocked by cold. Repetition of the epinephrine injections then failed to cause fibrillation (two injections in each animal). After allowing the vagi to rewarm to body temperature (33° and 27°C.) epinephrine again incited fibrillation. Two animals with the vagi cut in the neck failed to fibrillate in four trials with epinephrine.

Effects of Vagus Stimulation Following Epinephrine Injection.—This combined procedure proved more effective in producing fibrillation than did either vagus stimulation or epinephrine injection alone. In the seven dogs of this series, only two hearts failed to fibrillate. These two received epinephrine by slow

intravenous drip at a rate of 1.0 to 4.0 micrograms per kilogram per minute over a period of two hours, during which time the vagi were stimulated at intervals.

In none of the seven dogs did epinephrine alone induce fibrillation. In one, fibrillation was induced without epinephrine only on the first of sixteen periods of stimulation of the right vagus. In the fifteen minutes following injection of epinephrine, 0.07 mg. per kilogram, stimulation of the right vagus resulted in fibrillation in four successive trials. The following three periods of stimulation were ineffective; then fibrillation was again produced by vagus stimulation after repetition of the epinephrine injection. In the same dog, application of 1:1,000 epinephrine to the outside of the auricle before or during right vagal stimulation did not cause fibrillation.

Right vagus stimulation following epinephrine injection was successful in three other dogs, the ratios of successes to trials in these dogs being 4:13, 3:5, and 2:8. In none of these dogs was stimulation of the left vagus effective.

In the fifth success of this series, right vagus stimulation was ineffective, but following epinephrine left vagus stimulation produced fibrillation once in seven trials.

DISCUSSION

The results show that epinephrine and the vagus nerves can act synergically to incite atrial fibrillation. It has been shown that vagomimetic drugs may incite fibrillation in the absence of other obvious contributory causes.[15] Our results suggest that the same may be true of vagus nerve stimulation. However, both these results may be complicated by simultaneous release of epinephrine-like substances in the heart[41,42] and also by anoxia resulting from prolonged ventricular arrest.[39] Epinephrine injections alone are also adequate to produce atrial fibrillation but seemingly only when the vagi are intact. It is possible that this response is due entirely to reflex vagus activation by the greatly increased arterial pressure and that the greater effectiveness of combined vagus stimulation and epinephrine injections is due to mutual reinforcement of vagus effects. But many reasons may be cited against this view: for example, (a) long periods of high arterial pressure associated with Pentothal anesthesia early in the experiments[38] never caused fibrillation, nor did aortic occlusion; (b) small doses of epinephrine uniformly failed to produce fibrillation although the increase of blood pressure frequently approached that caused by effective doses; and (c) fibrillation was sometimes induced in advanced hypothermia when epinephrine failed to raise arterial pressure above the normal before cooling. It seems more probable that the synergic effect is due to a direct action of epinephrine on the atrial muscle, comparable to that of thyroid hormone.[20,30]

As to the nature of this epinephrine effect we have no information, but it is reasonable to suppose that it acts through promoting atrial extrasystoles during vagus inhibition of the sinus node. The possibility of an indirect action, perhaps through circulatory embarrassment and atrial distension,[39] is suggested by the fact that fibrillation following epinephrine injections alone does not usually begin

until blood pressure has begun to fall, and also by the fact that very large doses of epinephrine are required. Mines[43] in elaborating the "circus motion" theory of fibrillation suggested that two conditions are necessary for atrial fibrillation to develop: (1) a decreased refractory period; and (2) a decreased conduction rate in atrial muscle. Stimulation of the vagus nerve has been shown to satisfy the first of these conditions[9,44] but not the second.[9] Epinephrine also reduces the refractory period moderately[44] but greatly increases the intra-auricular conduction rate.[45] We have found that fibrillation is most likely to occur under vagus stimulation during complete sinus arrest. The site of excitation must therefore be an ectopic atrial one or the A-V node. Epinephrine greatly increases the likelihood of discharge from ectopic sites and it is to this action that we attribute its direct action in promoting atrial fibrillation. Van Dongen[46,47] has shown that the fibrillation-inhibitory potency of various drugs is associated with their capacity to prevent heterotopic rhythms rather than with their ability to alter the refractory period or conduction time of atrial muscle; hence drugs which excite atrial extrasystoles may be expected to facilitate the development of fibrillation.

These experiments provide no clue to the cause of atrial fibrillation in hypothermia in man. While exposure to cold promotes release of small amounts of epinephrine in the cat[48] and hypothermia protects epinephrine against detoxification,[49] it is most unlikely that adequate amounts accumulate in the blood stream of severely cooled men. The responses of the heart and peripheral vessels to epinephrine are well preserved in hypothermia, but all accounts agree that arterial pressures and heart rates are decidedly reduced at the temperatures conducive to fibrillation. Avoidance of anoxia in our experiments may have prevented spontaneous atrial fibrillation. Anoxia is known to favor fibrillation[39] and to sensitize the heart to vagus action.[50,51] Dill and Forbes[52] have shown that signs of anoxia begin to appear in the chilled human being at about the same temperature (30° C.) at which spontaneous fibrillation occurs.

SUMMARY

1. Atrial fibrillation has been produced in dogs subjected to various degrees of hypothermia by (a) vagus stimulation; (b) intravenous epinephrine injections; and (c) vagus stimulation following epinephrine injections.

2. Epinephrine injections produced fibrillation only when functional vagi were present and vagal stimulation following epinephrine injections was more effective than either procedure alone.

3. Epinephrine is believed to cause fibrillation (a) by causing reflex vagus excitation; and (b) by exciting ectopic atrial extrasystoles.

4. There is no evidence that hypothermia affected the production of atrial fibrillation by these means.

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ELECTROCARDIOGRAPHIC CHANGES ON TILTING

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IMPORTANT cardiovascular adjustments take place on change of position. It has long been known that changes in the length of the cardiac cycle occur. However, studies on the relationship of systole to the cycle have, in general, been inconclusive. Lombard and Cope[1] first noted that systole was shorter in relation to the cycle in the standing than in the sitting or lying posture. Cheer and Li[2] and White, Kossmann, and Erschler[3] also found that systole was shorter in relation to the cycle in the sitting position than lying at rest, but in neither case was the difference statistically significant. White and Mudd[4] found that systole and cycle were both shortened proportionately in the standing position. Schlamowitz[5] has recently reported that there was no significant difference in the two positions. Horwitz and Graybiel[6] found that on tilting to 60° from the horizontal, systole was long in relation to the cycle. In the present study the changes in systole/cycle relationship on tilting to the vertical and again on returning to the horizontal have been investigated in greater detail in men exposed to some cardiovascular stress. In particular, the time relations have been examined and the effect on the changes of alterations in environmental conditions.

METHODS

During studies of the effect of various procedures on the performance of men in the heat, reaction to tilting was used as one measure of performance.

The details of the experimental methods are given elsewhere.[7] In brief, there were two series of experiments. In the first, conducted during the months of July and August, four young men (medical students) were kept for periods of about twenty-eight hours in a psychrometric room. They entered the room at 8 A.M., dressed themselves in shorts, undershirts, and sandals, and remained there until about noon of the next day. This was done two or three times a week, control and experimental periods being alternated. During the control periods the temperature was maintained at 33°C. (dry bulb) and 28 to 29°C. (wet bulb) (hot) throughout. Tests of performance were begun at about 8 A.M. on the second day with the subjects in a basal state. During the experimental periods the following changes were made: (a) the room was maintained at 20°C. (dry bulb) and 18°C. (wet bulb) from 8 A.M. on the first day until 5 A.M. on the second day

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(cold experiment); (b) the room was kept hot, but the subjects remained lying throughout the first twenty-four hours until tests were made, except for essential toilet (rest experiment); (c) the room remained cold as in (a) and the subject remained lying as in (b) (cold and rest experiment); (d) 500 c.c. of blood was removed from each subject about twelve hours before testing. In every case tests were done at the same (hot) temperature.

In the second set of experiments, conducted during the fall, four somewhat older men served as subjects. They entered the room (maintained at the same hot temperature as in the summer experiments) in a basal state in the morning. Tests were begun after one hour's rest. After testing, the subjects lay down for another hour, and the tests were then repeated. On the experimental days certain procedures were done during the hour's rest. On one day 100 c.c. of a 25 per cent solution of serum albumin were given intravenously,* and on another day 200 c.c. of blood were withdrawn.

All of the subjects were healthy men with no known cardiovascular disease. In order to make performance as uniform as possible all subjects (except R. D.) had considerable practice on the tilt table before the actual series of experiments were begun. Subjects were tested in the same order on every day as far as possible.

The procedure for testing on the tilt table was as follows: The subject lay down for one hour. Active standing was then tested (Crampton test). The subject then mounted the tilt table and lay down. The table used was a simple structure fitted with a foot board and a band to be tied across the chest. Electrocardiograph leads were attached and after about ten minutes, or when the heart rate had settled down to a steady level, the subject was tilted to 70° from the horizontal. Tilting was done as evenly and swiftly as possible by a trained operator, and usually lasted about two seconds. After tilting to the vertical, the subjects remained as still as possible, breathing regularly. At intervals they gave brief replies to questions about the presence of symptoms. They were maintained in the vertical position for twenty minutes and then returned to the horizontal position. If fainting seemed imminent they were returned to the horizontal before the twenty minutes were finished. They were observed for a further five minutes in the horizontal position.

Electrocardiograph records were taken before and during tilting, and immediately, thirty seconds, sixty seconds, three, five, ten, fifteen, and twenty minutes after tilting. In the first series of experiments the three-, ten-, and fifteen-minute records were not obtained. Records were again taken during, immediately after, and thirty seconds, sixty seconds, three minutes (not in the summer experiments), and five minutes after return to the horizontal.

In most subjects Lead II was used. In Subjects E. B. and J. W. Lead I was used, since Q-T intervals could not be measured accurately on Lead II. In one subject in the first experiment measurements could not be adequately made on any lead, and he was, therefore, excluded from the results.

*Serum albumin was kindly given by the American Red Cross.

The electrocardiograph used was the Sanborn portable Cardiette. It ran consistently less than 1 per cent fast.

Tracings were taken at each stated time for about five seconds. Systole (beginning of Q to the end of T) and diastole (end of T to beginning of Q) were measured for five cycles and mean values used. It was found that fluctuations in cycle length were present even at rest and were usually no greater at times when the heart rate was changing. From the mean figures of systole and cycle, K was calculated for each time from Bazett's formula[8] ($systole = K\sqrt{cycle}$, or $K = \frac{systole}{\sqrt{cycle}}$). The accuracy of measurement was to 0.01 second. This gives a limit of error for K of 10 where K is 376 (intermediate value), 12 where K is 336 (low value), and 13 where K is 413 (high value). In general, at a given cycle length, if K is high, systole is long in relation to the cycle, while if K is low, systole is short in relation to the cycle.

RESULTS

The mean value of K at rest for all controls was 386. One subject (M. B.), whose mean was 412, gave consistently high values at rest.

In the control periods of the first experiment (Table I) consistent changes in K were found on tilting to the vertical and again on returning to the horizontal. On tilting to the vertical the mean value of K was significantly* increased immediately and at thirty and sixty seconds after tilting. The maximum increase was obtained immediately in all three subjects. The K values obtained at five and twenty minutes are suggestively but not significantly greater than the initial values. The five- and twenty-minute values are significantly less than the immediate, the thirty-second, and the sixty-second ones, but the values in these two groups are not significantly different from each other. On returning to the horizontal, the immediate, the thirty-second, and the sixty-second values are significantly less than the initial value and greater than the five-minute value. There is no significant difference between the first three values, and the five-minute value is not significantly less than the resting value. The maximum decrease was at thirty seconds in two subjects and immediately in one.

Similar results were obtained in the control periods of the second set of experiments (Table II). On tilting to the vertical, K was significantly greater than the initial value at all times except at ten and twenty minutes. However, maximum increases were obtained at sixty seconds in one subject, at thirty seconds in one, and at both in one, while in one (C. S.) no thirty-second values were obtained for comparison. The three-, five-, ten-, fifteen-, and twenty-minute values were significantly less than the maximum value (thirty seconds), but

*A difference is here considered significant if the possibility of obtaining by chance a difference as great as or greater than that observed is less than 1:100, that is, if the actual difference between the two means is greater than 2.60 times the standard error of the difference between them. This assumes random sampling.

Table I. Resting Values of K and Changes in K After Tilting in Control Periods (First Experiment)

Date	Subject	K at rest	After tilting to the vertical: Immed.	30 sec.	60 sec.	5 min.	20 min.	After returning to the horizontal: Immed.	30 sec.	60 sec.	5 min.
7–18	R. A.	365	+27	+ 7	+ 9	+15	+13	0	−34	−25	+ 3
7–22	R. A.	364	+23	+14	+29	+ 9		+ 3	−62	−68	− 8
7–26	R. A.	367	+40	+13	+15	+ 6	+30	− 4	−26	−30	−10
7–31	R. A.	373	+39	+30	+17		+24	−13		−21	+ 9
8–12	R. A.	395	+31	+18	+ 5	+16	+ 6	−22	−56	−51	−36
8–22	R. A.	369	+37	+28	+11	+10	+12	−45	−33	−47	− 8
	Means	372	+33	+18	+14	+11	+17	−14	−42	−40	− 8
7–18	M. B.	412	+28	+28	+13	+ 6	− 4	−58	−18	−32	+ 3
7–22	M. B.	393	+33	+22	+25	− 2	+14	− 8	−53	−33	+16
7–26	M. B.	393	+29	+50	+53	+27	+32		−29	−20	+17
7–31	M. B.	430		+24	+25	+15			−55	−37	− 8
8–5	M. B.	430		+11	+ 4	+ 4	− 6	−76	−61	−52	−15
8–12	M. B.	420	+23	+23	+23	− 5	+ 2	−69	−59	−32	+10
8–22	M. B.	404	+12	+ 9	+20	+20	+29	0	−29	−29	−16
	Means	412	+25	+24	+23	+ 9	+11	−42	−43	−34	+ 1
7–26	R. D.	380	+48	+20	+14	+30	+17	−69	−29	−27	−19
7–31	R. D.	402	+14	+26	+31	+ 7	+41		−48	−50	− 8
8–5	R. D.	364	+49	+67	+26	+44	+ 6	−50	−32	−31	− 2
8–8	R. D.	392	+30	+25	+18	+16	+18	−85	−50	−41	−23
8–22	R. D.	397	+19	+19	+27	+18	+27	−57	−68	−84	−28
	Means	387	+32	+31	+23	+23	+22	−65	−45	−47	−16
	Means (First exp.)	392	+30	+24	+20	+14	+16	−37	−44	−39	− 7
	σ	22	11	15	11	12	14	32	15	17	15

TABLE II. RESTING VALUES OF K AND CHANGES IN K AFTER TILTING IN CONTROL PERIODS (SECOND EXPERIMENT)

DATE	SUBJECT	K AT REST	AFTER TILTING TO THE VERTICAL								AFTER RETURNING TO THE HORIZONTAL				
			IMMED.	30 SEC.	60 SEC.	3 MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	IMMED.	30 SEC.	60 SEC.	3 MIN.	5 MIN.
11–13	E. B.	384	+10	+41	+61	+36	+20				−17	−51	−51	−17	−19
11–17	E. B.	384	+37	+55	+45	+10	+13	+13			−48	−74	−41	−22	−25
11–20	E. B.	376	+42			+31			+23			−50	−36		−17
	Means	381	+30	+48	+53	+26	+17	+13	+23		−33	−58	−43	−20	−20
11–6	M. N.	374	+39	+50	+41	+33	+23	+11	+38		−54	−17	−19	−10	− 4
11–14	M. N.	374	+45		+51	+29	+11	+29	+45	+36	−44	−35	−17	+18	+19
11–18	M. N.	380	+26	+39	+45	+12	+15	+24		+26	−23	−27	−21	−13	+ 3
11–21	M. N.	381	+27	+41	+28	+25	+13	+16	+16		−50	−49	−28	−17	+ 5
11–24	M. N.	403	+19	+24	+29	+27	+ 7		0	+ 7	−92	−49	−25	− 7	−29
	Means	382	+32	+39	+39	+25	+14	+20	+25	+23	−53	−35	−22	− 6	− 1
11–16	C. S.	384	+32			−18	+ 2				0	−12	−35	−24	− 5
11–14	C. S.	371	+39		+15	− 6	0				+ 7	−13	−25	+ 4	− 9
11–18	C. S.	395	+31				−16	−24		−27	−64	−44	−37	−14	−10
11–21	C. S.	380	+32								−23	−20	−39	−25	−13
	Means	383	+34		+15	−12	− 5	−24		−27	−20	−22	−34	−15	− 9
11–5	J. W.	367	+57		+12		+27		+27	− 2	−44	−52	−40	− 2	− 4
11–13	J. W.	379	+21	+43	+24	+ 8	+24	+ 9	+24	+18	−81	−57	−34	−28	−25
11–17	J. W.	371	+45	+60	+39	+ 9	+17	+43	+47	+42	−62	−28	−20	− 7	+ 5
11–20	J. W.	390	+32	+34	+41	+ 5	+12	+12	−15	+22	−73	−77	−37	−27	−17
11–24	J. W.	379	+39	+48	+15	+18	+21	+18	+21	+28	−75	−68	−24	+ 1	+ 3
	Means	377	+39	+46	+26	+10	+20	+21	+21	+22	−67	−56	−31	−13	− 8
	Means (Second exp.)	381	+34	+44	+34	+16	+13	+15	+23	+17	−46	−43	−31	−12	− 8
	σ	9	11	10	15	13	11	17	19	21	29	21	9	13	13

showed no significant differences among themselves. There were also no significant differences between the immediate, the thirty-second, and the sixty-second values. On returning to horizontal, the immediate, the thirty-second, the sixty-second, and the three-minute values are significantly less than the initial value, while the five-minute value is not significantly less. There is no difference between the first three values or between the last two, but the latter are significantly greater than the former. The maximum decrease was at thirty seconds in one and immediately in two subjects.

In the experimental periods (Tables III and IV), the changes in K followed a course similar to that observed in the control periods. Mean values for three subjects in the first experiment and four subjects in the second experiment did not at any time show a significant difference from the control figures (more than three standard deviations from the mean). An apparently greater increase in K on tilting to the vertical and less decrease on returning to the horizontal position in the "rest" experiment is probably connected with the fact that the initial value of K in each subject was lower than usual. Converse changes are seen in the "cold and rest" experiment.

In Table V the mean changes in K are compared with the mean changes in pulse rate in the control periods of both sets of experiments. The changes are in the same direction in most instances, but the time relations and magnitude are very different.

Table VI shows the values of K obtained after tilting in two subjects, (1) twenty-five minutes after the subcutaneous injection of atropine sulfate (grain 1/50) and (2) fifteen minutes after the subcutaneous injection of ergotamine tartrate (0.5 mg.). The resting value of K is slightly increased after atropine. On tilting to the vertical after ergotamine, the increase in K is not as great as usual. On returning to the horizontal the decrease in K is less than usual after ergotamine, and greater than usual after atropine. These differences are not statistically significant, even though suggestive.

The T waves in all subjects were reduced in size after tilting to the vertical and returned to normal after return to the horizontal position. In two subjects (E. B. and J. W.) the T waves in Lead II disappeared or became inverted on tilting to the vertical. In Lead I the changes were in the same direction but less marked. In general, the height of the T waves appeared to vary inversely with the heart rate, but observations were not sufficiently accurate or numerous to admit of definite conclusions.

Immediately after returning to the horizontal position, prolonged diastoles (over 1.25 seconds) were noted in several instances, and on one occasion an extrasystole was seen in a subject who was never observed to have had an extrasystole before. No other abnormalities were seen.

Observations after exercise in two subjects (R. A. and M.. B.) showed an average K value of 398 at four minutes, 387 at five minutes, and 410 at seven minutes after work on the bicycle ergometer. Pulse rates at the same times averaged 122, 125, and 116 beats per minute, respectively. These K values are not significantly different from those obtained at rest.

TABLE III. MEAN VALUES OF K ON LYING AT REST AND MEAN CHANGES IN K ON TILTING IN THREE SUBJECTS IN CONTROL AND EXPERIMENTAL PERIODS (FIRST EXPERIMENT)

EXPERIMENT	LYING AT REST	AFTER TILTING TO THE VERTICAL					AFTER RETURNING TO THE HORIZONTAL			
		IMMED.	30 SEC.	60 SEC.	5 MIN.	20 MIN.	IMMED.	30 SEC.	60 SEC.	5 MIN.
All controls	392	+30	+24	+20	+14	+16	−37	−44	−39	− 7
σ controls	22	11	15	11	12	14	32	15	17	15
a. Cold	386	+31	+26	+15	+ 9	+22	−21	−44	−44	− 6
b. Rest	374	+52	+31	+35	+35	+51	− 4	−12	−36	+ 6
c. Cold and rest	412	+13	+12	0	− 1	− 3	−90	−66	−47	−28
d. Hemorrhage + 12 hours	405	+25	+34	0	+11	+13	−70	−53	−47	−10
Hemorrhage +84 hours	387	+39	+27	+24	+19	+17	−61	−38	−32	+ 2

TABLE IV. MEAN VALUES OF K ON LYING AT REST AND MEAN CHANGES IN K ON TILTING IN FOUR SUBJECTS IN CONTROL AND EXPERIMENTAL PERIODS (SECOND EXPERIMENT)

EXPERIMENT	LYING AT REST	AFTER TILTING TO THE VERTICAL							AFTER RETURNING TO THE HORIZONTAL				
		IMMED.	30 SEC.	60 SEC.	3 MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	IMMED.	30 SEC.	60 SEC.	3 MIN.	5 MIN.
All controls (early A.M.)	381	+34	+44	+34	+16	+13	+15	+23	+17	−46	−43	−31	−12	− 8
σ controls	9	11	10	15	13	11	17	19	21	29	21	9	13	13
Controls (late A.M.)	378	+34	+43	+34	+25	+19	+19	+27	+25	−57	−31	−26	− 9	+ 4
After infusion	373	+31	+44	+32	+16	+21	+17	+21	+12	−36	−43	−22	− 9	−10
After hemorrhage	381	+30	+38	+43	+16	+18	+19	+22	+22	−61	−49	−41	−22	− 2

TABLE V. COMPARISONS OF MEAN INCREASES IN PULSE RATE AND INCREASE IN K VALUES IN CONTROL PERIODS

First Experiment

	IMMED.	30 SEC.	60 SEC.	5 MIN.	20 MIN.
After Tilting to the Vertical					
K	+30	+24	+20	+14	+16
Pulse rate	+17	+22	+26	+28	+33
After Tilting to the Horizontal					
K	−37	−44	−39	− 7	
Pulse rate	+ 4	− 9	−12	− 6	

Second Experiment

	IMMED.	30 SEC.	60 SEC.	3 MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.
After Tilting to the Vertical								
K	+34	+14	+34	+16	+13	+15	+23	+17
Pulse rate	+15	+27	+34	+36	+34	+31	+33	+33
After Tilting to the Horizontal								
K	−46	−43	−31	−12	− 8			
Pulse rate	+ 1	− 5	− 7	− 8	− 6			

DISCUSSION

Various formulas have been suggested relating systole to the cardiac cycle. Frequent use has been made of Bazett's formula which is used in this study. Schlamowitz[9] in a study of 650 normal men has compared several formulas. He found that the relationship between systole and cycle at rest was linear rather than curvilinear. However, Bazett's formula fitted the data reasonably well, especially at rapid heart rates. In the present study relative rather than absolute changes were of interest, and the discrepancies in Bazett's formula may be ignored since it provides a convenient relative index of systole/cycle relationship.

In experimental animals various factors have been found to affect K (or systole/cycle). Katz[10] and Wiggers[11] showed that systole was prolonged by increase of the venous return to the heart. Recently Robb and Turman[12] have shown in intact dogs that the Q-T/cycle relationship is reduced by stimulation of the vagus, chiefly through the lengthening of diastole. Injection of atropine increased Q-T/cycle (presumably by inhibiting vagal action), while injection of adrenalin caused a vagal reflex and in the atropinized animal increased the Q-T/cycle value, mainly by shortening diastole. Adrenalin may also shorten systole directly.[11]

TABLE VI. RESTING VALUES OF K AND CHANGES IN K AFTER TILTING FOLLOWING INJECTION OF ATROPINE AND ERGOTAMINE TARTRATE

SUBJECT	LYING BEFORE INJECTION	25 MIN. AFTER INJECTION	AFTER TILTING TO THE VERTICAL								AFTER TILTING TO THE HORIZONTAL				
			IMMED.	30 SEC.	60 SEC.	3 MIN.	5 MIN.	10 MIN.	15 MIN.	20 MIN.	IMMED.	30 SEC.	60 SEC.	3 MIN.	5 MIN.
Atropine															
E. B.	388	418	+ 6	+44	+25	+29					+ 5	−15	−41	+ 4	+ 1
M. N.	404	407	+27	+26	+25	+21	+15	+20	+20	+15	− 5	−29	0	+17	+ 7
Means	396	413	+17	+35	+25	+25					0	−22	−21	+11	+ 4
Ergotamine															
		15 MIN. AFTER INJECTION													
E. B.	394	394	+14	+26	+13	− 6		+ 3	+16		−15	−57	−56	−44	−37
M. N.	389	406	+31	+16	+ 1	−23	−29	−25	−19		−60	−48	−77	−55	−28
Means	387	400	+23	+21	+ 7	−15		−11	−2		−38	−53	−67	−50	−33

On tilting from the horizontal to the vertical position, changes in the filling of the heart and in its nervous control must occur. The consistent results obtained in these experiments, that is, a relative lengthening of systole on tilting to the vertical with a subsequent return to almost the initial relationship, and a relative shortening of systole on returning to the horizontal with a return to the initial value after three to five minutes, may be tentatively explained as follows. An early reduction in vagal tone (shortening of diastole) may be followed by a later increase in sympathetic tone (shortening of systole). On returning to the horizontal position the changes are reversed, a sudden return of vagal tone being followed by a slow decrease of sympathetic activity. However, this scheme does not account for the mechanical changes of venous return which is presumably reduced on tilting to the vertical and increased on returning to the horizontal. Also, the changes in sympathetic tone might conceivably be expected to occur earlier than three minutes after tilting. Although the effect of the vagus upon ventricular systole has been questioned, some evidence for the role of the vagus was given by the atropine experiment. Here the resting value of K was high and the decrease on returning to the horizontal was less marked, indicating that full vagal control did not return. Ergotamine tartrate may potentiate the action of the vagus in the heart.[13] The smaller increase in K after tilting to the vertical and the larger decrease after returning to the horizontal support this.

Changes in blood volume might be expected to affect the adjustment of the heart to the strain of tilting. Blood volume has been shown to be reduced by cold[4] and rest.[15] In the experimental periods of the first series of experiments blood volume was reduced by cold, rest, cold and rest, and hemorrhage. In the second series it was increased by infusion and decreased by hemorrhage. The probable amounts of change so produced are discussed elsewhere,[7] but in any case did not exceed 8 to 10 per cent of the total blood volume, and were usually less than that. In general, performance was correlated with the changes in blood volume. Performance on the tilt table was measured by the average of the fifteen-, seventeen-, and nineteen-minute pulse rates obtained after tilting to the vertical, or, if the subject approached fainting, by the maximum pulse rate obtained. In the first series cold, cold and rest, and hemorrhage produced a higher pulse rate (worse performance); rest gave equivocal results. In the second series of experiments infusion produced a lower pulse rate (better performance) in all four subjects; hemorrhage produced a higher rate in two, a lower rate in one, and no change in the fourth subject. Performance in the other tests paralleled that on the tilt table. No similar alterations in the changes of the systole/cycle relationship were observed. In the absence of more extensive studies, it is likely that in normal men: (1) the changes in systole/cycle relationship which occur on tilting in the heat are not affected by procedures which alter blood volume by small but definite amounts, and (2) the factors affecting the systole/cycle relationship are not the same as those affecting the pulse rates reached after tilting.

In the summer experiments the subjects were probably partly acclimatized to the temperatures used for the tests. In the second experiment the subjects were definitely not acclimatized. The values of K at rest did not differ significantly in the two experiments (though the mean for the second experiment

was slightly lower than that for the first). In the second experiment, however, the maximum increase of K occurred later than in the first experiment. The exact significance of this is not obvious.

SUMMARY

1. Electrocardiograms were taken before, during, and after tilting in normal young men in the heat.

2. In control experiments systole was found to be long in relation to the cycle after tilting to the vertical and to be reduced, though not to the initial value, after three minutes. On returning to the horizontal position, systole was short in relation to the cycle and began to approach the resting value after three minutes.

3. These changes were not affected by procedures which altered blood volume and performance by small but definite amounts, that is, bed rest, exposure to cold, hemorrhage, or infusion of serum albumin.

4. Some evidence for the possible role of the vagus in these changes is presented.

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QUANTITATIVE STUDIES OF VENTILATION DURING INHALATION OF CARBON DIOXIDE IN NORMAL AND EMPHYSEMATOUS PATIENTS

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THAT the respiratory center is very responsive to small increments of rapid changes in carbon dioxide tension was demonstrated in the years 1903 to 1905, and recorded in 1905 in a paper by Haldane and Priestley.[1,b] To quote from their paper: "The respiratory center is exquisitely sensitive to any rise in the alveolar carbon dioxide pressure, a rise of 0.2 per cent of an atmosphere in the alveolar carbon dioxide pressure, for instance, being sufficient to double the amount of alveolar ventilation during rest." Two-tenths per cent of an atmosphere is equivalent to an increase in tension of 1.52 mm. Hg of carbon dioxide, or a decrease in pH of 0.012 in Haldane's patients.

Nielsen[2] in 1936 recorded similar studies and reported an increase of 10 liters of ventilation per minute for an average decrease in pH of the arterial blood of 0.02 in one patient, and 0.045 in another. Krogh[3] has also shown in one patient an increase of 10 liters in ventilation for decrease in pH of the arterial blood of 0.04 to 0.045, and of a second patient 10 liters increased ventilation per minute for a change of 0.02 in the arterial blood pH.

There are no serious objections to the methods that these different groups of investigators used in studying normal subjects. Haldane and Priestley incased the patient in a body plethysmograph, and by means of a small tube connecting the plethysmograph to a kymograph drum were able to record tidal air, rate, and minute volume. Around the individual's head was a chamber which allowed the patient to rebreathe his own exhaled air. This was devised in such a manner that samples of alveolar air could be collected at will for an analysis of carbon dioxide tension.

Nielsen's group[2] utilized a different technique and measured arterial blood for total carbon dioxide content and alveolar air for carbon dioxide tension. By this method they calculated arterial blood pH by utilizing the Henderson-Hasselbalch equation, assuming arterial blood carbon dioxide tension to be in equilibrium with alveolar carbon dioxide tension. They were also able to measure the tidal air, rate, and minute ventilation, since the patient was breathing into a spirometer.

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Scott[4] and Meakins and Davies[5] have both reported that emphysematous patients were insensitive in their response to the inhalation of high percentages of carbon dioxide, as compared with normal subjects. These investigators also calculated blood pH, since they measured alveolar carbon dioxide tension and total serum bicarbonate.

The present study was undertaken to see if these quantitative studies on normal subjects could be reduplicated by using a different technique (direct measurement of blood pH), perhaps better suited for the study of pathologic states as encountered in diseases as, for example, emphysema, congestive heart failure, and bronchial asthma.

TECHNIQUE

The patients were brought into a quiet room where they assumed the supine position on a comfortable bed. They were allowed to breathe into a Benedict-Roth type spirometer for some time, until they became adjusted to it. The pointer was connected to a rotating smoked drum, moving at a constant speed of 5.2 cm. per minute. The spirometer contained 30 per cent oxygen and 70 per cent nitrogen. Tidal air, rate, and minute ventilation were recorded on the drum while the patient breathed into the spirometer. At the time the spirometer contained 22 to 25 per cent oxygen, an arterial puncture was made into one femoral artery and two samples of blood collected: one under oil, with sodium oxalate, for determination of oxygen content, and the second under oil, without sodium oxalate, for determinations of pH and total carbon dioxide content of the serum. Oxygen content and capacity studies were done only on the patients with emphysema and fibrosis of the lungs.

After the blood had been collected, the soda lime was taken out and 30 per cent oxygen, 3 per cent carbon dioxide, and 67 per cent nitrogen were added to the spirometer, and the patients were allowed to rebreathe (with the soda lime removed) into the spirometer. After a marked increase in ventilation, which was, in every instance, before the patient's maximal effort was reached, a second femoral artery puncture was done and blood collected for serum pH and total serum carbon dioxide. Twenty-five minutes was about the average time required for completion of an experiment.

The blood gases were analyzed by the method of Van Slyke and Neill.[6] The pH of the arterial blood was determined by means of a Coleman pH electrometer, with a glass electrode attachment. The data used to plot Chart I were obtained by having two normal subjects at rest (not basal) respire into a Benedict-Roth type spirometer at selected rate and tidal exchange.

Two groups of patients were studied: (1) twelve normal, healthy young male adults; (2) thirteen patients with pulmonary disease, which included twelve emphysematous patients, and one patient with fibrosis of the lung (Boeck's sarcoid).

RESULTS

I. *Normal Subjects.*—In the twelve normal subjects there was considerable variation in the ventilation, expressed in liters increase per minute for each millimeter increase in carbon dioxide tension (Tables I and II). This ranged from a low of 0.72 liters in one subject to a high of 9.89 liters in a second subject. The average increase in ventilation per minute of the twelve subjects was 2.71 liters, with 1.60 liters per minute increase as the median value of this group. In

TABLE I. NORMAL SUBJECTS: RESTING

NAME	MIN. RESP. RATE	TIDAL AIR (C.C.)	MINUTE VENTILATION (LITERS)	ARTERIAL BLOOD pH	SERUM CO_2 TENSION (MM.HG)	TOTAL SERUM CO_2 (VOL. %)	VITAL CAPACITY (C.C.)	VENTILATION / VITAL CAPACITY
B. B.	13	746	9.68	7.58	28.3	59.3	4,600	2.10
J. F.	16	904	14.46	7.58	26.5	55.4	4,000	3.62
H. M.	16	479	7.62	7.47	33.8	55.3	3,820	2.00
D. B.	12	436	5.20	7.58	29.5	61.8	4,650	1.12
T. S.	14	622	8.72	7.44	29.0	44.6	4,405	1.98
R. R.	16	593	9.49	7.41	41.3	59.2	4,050	2.34
C. W.	16	664	10.6	7.38	46.0	62.0	4,520	2.35
F. N.	13	768	10.00	7.37	44.0	57.6	4,210	2.38
W. C.	13	664	8.63	7.38	43.9	59.0	4,015	2.15
S. B.	14	519	7.27	7.32	51.0	60.2	4,195	1.73
W. R.	20	415	8.30	7.47	36.5	59.8	4,420	1.88
H. Mc.	25	509	12.74	7.57	25.4	52.0	4,230	3.01
Median								
Average				7.46	36.3	57.01		

TABLE II. NORMAL SUBJECTS DURING CARBON DOXIDE HYPERPNEA

NAME	MIN. RESP. RATE	TIDAL AIR (C.C.)	VENTILATION (LITERS PER MIN.)	ARTERIAL BLOOD pH	SERUM CO_2 TENSION (MM.HG)	TOTAL SERUM CO_2 (VOL. %)	MINUTE VENTILATION INCREASE PER MM. HG OF CO_2	MINUTE VENTILATION INCREASE PER .01 pH
B. B.	25	2,480	62.02	7.48	36.5	61.3	6.38	5.23
J. F.	36	1,856	66.90	7.53	31.7	59.4	10.00	10.4
H. M.	21	974	20.45	7.34	49.4	60.8	.82	.98
D. B.	24	791	18.96	7.52	35.4	64.9	2.30	2.29
T. S.	25	1,390	34.75	7.34	40.2	49.5	2.34	2.60
R. R.	22	1,015	22.35	7.38	45.0	60.6	3.47	4.27
C. W.	24	1,610	38.65	7.28	62.1	67.3	1.75	2.80
F. N.	19	913	17.35	7.32	53.4	63.0	.78	1.47
W. C.	14	1,245	17.44	7.33	53.1	64.0	.96	1.76
S. B.	25	891	22.25	7.26	63.2	65.6	1.23	2.50
W. R.	25	1,140	28.50	7.38	50.3	67.8	1.45	2.23
H. Mc.	25	1,763	44.10	7.36	50.4	64.9	1.25	1.49
Median							1.60	2.50
Average							2.71	3.16

terms of pH this shows an average increase of 3.16 liters per minute for 0.01 change in pH, and a median value of 2.50 liters.

II. *Patients With Emphysema and One Patient With Fibrosis of Lungs.*—Like the normal subjects, the patients with emphysema varied considerably in the increased amount of ventilation expressed in liters per minute per millimeter of carbon dioxide tension change (Tables III and IV). These patients had a low

TABLE III. EMPHYSEMA: RESTING

NAME	MIN. RESP. RATE	TIDAL AIR (C.C.)	MINUTE VENTILATION (LITERS)	ARTERIAL BLOOD pH	SERUM CO_2 TENSION (MM.HG)	TOTAL SERUM CO_2 (VOL. %)	SATURATION ARTERIAL BLOOD (PER CENT)	VITAL CAPACITY (C.C.)	VENTILATION / VITAL CAPACITY
C. W.	28	850	23.80	7.42	28.5	41.8	82.1	2,200	10.80
W. Z.	22	751	16.50	7.38	51.0	68.6	83.3	2,010	8.25
R. B.	18	477	8.60	7.40	46.4	65.2	86.2	1,206	7.16
B. J. W.	18	560	10.50	7.39	42.3	58.2	90.5	1,618	6.50
J. W.	20	456	9.11	7.50	31.6	55.4	74.6	1,605	5.68
F. Mc.	15	456	6.85	7.51	39.1	70.0	87.2	1,285	5.34
R. G.	14	664	9.30	7.37	37.6	49.5	86.4	1,810	5.14
J. B.	30	446	13.36	7.48	35.5	59.6	86.3	2,080	6.45
C. W.	13	664	8.65	7.57	28.2	57.8	88.7	1,604	5.40
J. M.	15	415	6.23	7.42	54.8	80.6	80.3	1,208	5.18
J. C.	30	456	13.70	7.51	39.8	71.4	87.0	1,215	11.30
W. H.	11	790	8.70	7.45	35.8	56.3	84.2	1,750	4.98
E. E.	11	540	5.94	7.38	48.2	64.8	91.2	1,680	3.53
Median									
Average				7.45	39.9	61.5			

TABLE IV. EMPHYSEMA: CARBON DIOXIDE HYPERPNEA

NAME	MIN. RESP. RATE	TIDAL AIR (C.C.)	VENTILATION (LITERS PER MIN.)	ARTERIAL BLOOD pH	SERUM CO_2 TENSION (MM.HG)	TOTAL SERUM CO_2 (VOL. %)	MINUTE VENTILATION INCREASE PER MM. HG OF CO_2	MINUTE VENTILATION INCREASE PER .01 DECREASE pH
C. W.	38	872	33.10	7.39	30.7	42.3	4.20	3.10
W. Z.	31	788	24.40	7.34	56.8	70.2	1.36	1.98
R. B.	18	560	10.04	7.37	53.3	70.0	.23	.48
B. J. W.	18	788	14.16	7.36	45.5	59.8	1.14	1.22
J. W.	28	974	27.25	7.44	39.1	60.1	2.40	3.02
F. Mc.	20	605	12.10	7.37	56.3	74.2	.31	.38
R. G.	21	872	18.31	7.28	47.4	51.3	.91	1.00
J. B.	31	726	22.50	7.46	37.8	60.6	3.97	4.57
C. W.	15	1,100	16.50	7.51	35.0	62.6	1.15	1.31
J. M.	30	415	12.45	7.40	60.3	84.7	1.13	3.11
J. C.	30	726	21.78	7.49	41.7	71.4	4.25	4.04
W. H.	11	1,450	15.95	7.38	42.6	57.4	1.06	1.04
E. E.	20	1,036	20.72	7.32	55.8	66.0	1.95	2.40
Median							1.13	1.98
Average				7.42			1.85	2.12

of 0.23 liters increase per minute for each millimeter increase in carbon dioxide tension of arterial blood in one patient, to a high of 4.25 liters increase per minute for each millimeter increase in carbon dioxide tension in another patient. Expressed as an average, it would equal 1.85 liters increased ventilation per minute per millimeter of carbon dioxide tension increase, with 1.13 liters increased ventilation per minute as a median value. In terms of pH, the average change per 0.01 decline was 2.12 liters, with 1.98 liters increase in ventilation as the median figure.

DISCUSSION

Normal Patients.—The quantitative response to inhalation of a given amount of carbon dioxide in a group of twelve normal subjects corroborates previous studies, as done by Haldane,[7] Krogh,[3] and Nielsen,[2] all of whom used slightly different techniques in making their studies. Haldane's[7] patients showed an average increase of 3.0 mm. Hg in carbon dioxide tension in order to double ventilation. Since these patients required 8.55 liters per minute to double ventilation, our finding would compare favorably, as a 3.0 mm. increase in carbon dioxide tension would equal an average increase of 8.13 liters per minute. Krogh showed ten liters increase per minute in one patient for a decrease in pH of 0.02. A second patient required a change in the arterial blood in a magnitude of 0.04 to 0.045 decrease in arterial pH. The patients in this study showed ten liters increase for an average of 0.031 decrease in arterial blood pH.

There was a tendency at first for some of the patients to hyperventilate, on anticipation of the arterial puncture. J. F., a medical student, had a minute ventilation of 14.46 liters.

Emphysematous Patients.—The preceding normal patients were studied in order to set a standard base line for the sensitivity of the normal patient, so that one could compare them with patients with respiratory difficulties.

Roelsen[8] has shown that the composition of the alveolar air, when fractionated with the Sonne-Ejnar-Nielsen apparatus, varies somewhat more in emphysematous patients than in normal subjects. Scott[4] has shown that for a given concentration of inspired carbon dioxide the increase in minute ventilation is less in emphysematous than in normal subjects, and suggested that such patients are less sensitive to carbon dioxide. However, since the emphysematous lung is pathologically altered, it does not follow necessarily that the blood carbon dioxide tension has risen correspondingly to what it might in normal subjects for the same minute ventilation. For these reasons it was thought wise to check ventilation increase compared to changes in arterial blood carbon dioxide tension, and not to alveolar air samples during breathing of varying percentages of carbon dioxide in the inhaled air. Scott suggests that the increased tolerance which his patients show to carbon dioxide inhalation, över the normal patients, might be due, in part, at least, to the increased buffering power of the emphysematous patient's blood, which had a considerably higher carbon dioxide content than did the normal subjects whom he studied. For example, to change the pH of blood with a

total serum carbon dioxide content of 80 volumes per cent from a pH of 7.45 to a pH of 7.42 requires 3.6 mm. increase in carbon dioxide tension, whereas a 2.8 mm. increase of the carbon dioxide tension will change the hydrogen ion concentration by the same degree, when the total serum carbon dioxide content in the blood is 60 volumes per cent. Therefore, it will of necessity require a slightly higher tension of carbon dioxide to produce the same reduction in pH in those patients with high serum bicarbonate levels.

On comparing these thirteen patients with the normal subjects, it is seen that the group average is 33 per cent less responsive, in terms of ventilation, to carbon dioxide tension changes. From a statistical analysis, however, the standard error of the means is greater than the difference between the means. Therefore, the difference between the means does not seem to be significant. The average total carbon dioxide content of the normal subjects was 93 per cent that of the emphysematous patients.

The respiratory center can respond with impulses to the respiratory muscles, but since the emphysematous lung has lost its elastic tissue, ventilation differs from the normal in that in the latter a given amount of work produces a given tidal exchange; but not so in the emphysematous patients. Their breathing is inefficient in that a given amount of work usually causes a smaller tidal exchange.[9] In so far as one can estimate respiratory effort, from the expression

$$\frac{\textit{ventilation (in liters per minute)}}{\textit{vital capacity (in liters)}}$$ as described by Harrison and his associates,[10]

the emphysematous patients show a marked increase in resting respiratory effort as compared with normal subjects (Tables I and III).

As already stated, a statistical analysis seems to indicate that the difference in the ventilation response was not significant. However, a further attempt was made to determine whether the emphysematous patient, although showing a slightly smaller response to the carbon dioxide inhalation in terms of average increased ventilation per minute, may have used as much or more respiratory effort. This consideration is shown in Chart I, in which the *A* and *A′* curves represent oxygen consumption per minute in two normal subjects at various levels of tidal air (or ventilation per minute, since the rate was kept constant). It is seen that as the normal subjects' tidal air approached their vital capacities, they utilized an increased amount of oxygen, which, of course, is indicative of work expended to respire. Curve *B* represents the theoretical expected oxygen consumption curve for the emphysematous patients. The actual measurement was not possible, as the patients were dyspneic at rest and could not selectively increase tidal air at a given rate. In view of the fact that the normal subjects utilized more oxygen as their tidal air approached their vital capacities, it is obvious that the patients with emphysema (who had less than 50 per cent normal vital capacity) were utilizing more oxygen than the normal subjects when the two were breathing at the same tidal exchange. For example, to increase tidal air from 1,000 c.c. to 2,000 c.c. would require less than one-half as much increase in oxygen consumption as compared with the emphysematous patient.

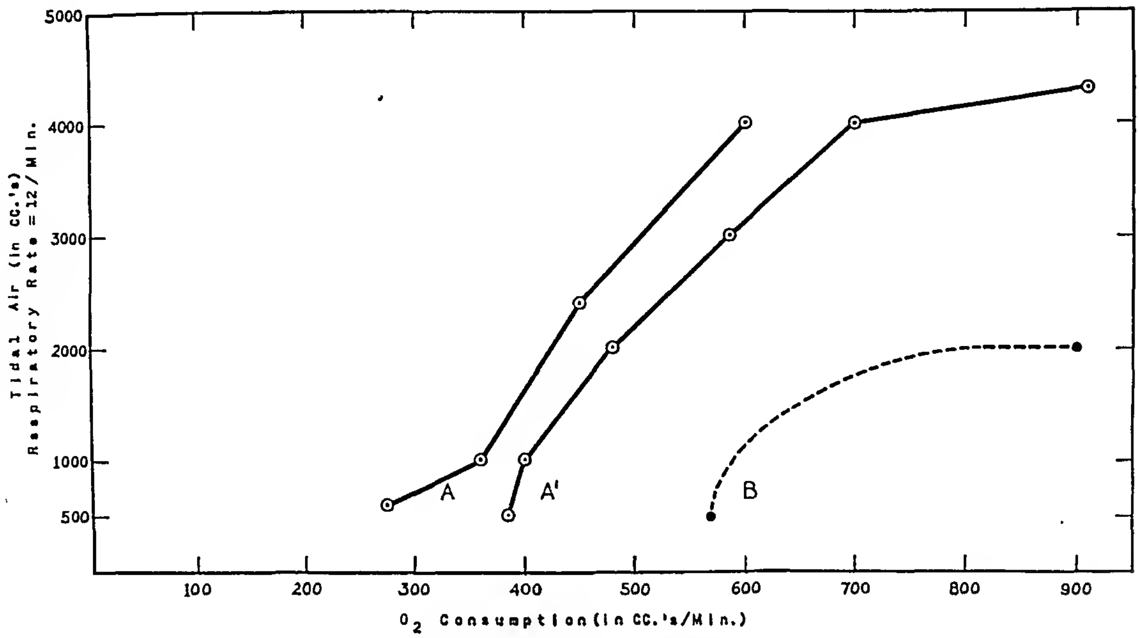

Chart I.—The oxygen consumed by two normal adult men under resting (but not basal) conditions is shown in relation to the tidal air. Since the rate was kept constant at a selected value by voluntary control, and since the subject's vital capacity was constant, the changes in tidal air represent corresponding changes in minute ventilation and in respiratory effort as measured by $\frac{\textit{ventilation}}{\textit{vital capacity}}$.

Curves *A* and *A'* represent actual data as obtained on two normal subjects. Curve *B* is theoretical and plotted for an emphysematous subject, because in such patients the severe dyspnea renders the actual measurement impossible.

It can be seen that for a given increment of ventilation the amount of increase in oxygen consumption becomes much greater as the subject approaches his vital capacity. It is, therefore, clear that in order to achieve a given increase in ventilation a markedly greater energy expenditure is necessary in the emphysematous patient, as compared with the normal subject.

Since the increase in oxygen consumption per minute is a good measure of respiratory effort under conditions of respiratory stress, it is obvious from the foregoing that, although the emphysematous patient responded with a slightly smaller increase in ventilation per minute, he may have actually expended a great deal more respiratory effort for the same increase in ventilation per minute than did the normal subject. This consideration was borne out, subjectively, by the patients, in that all of the emphysematous patients experienced rather marked subjective (and objective) respiratory distress at the levels of increased minute ventilation which caused no distress whatsoever in any of the normal subjects.

The slightly elevated average pH of the blood of the normal subjects was thought to be due to the fact that these subjects were anticipating an arterial puncture, and would hyperventilate at the time of the puncture. In reviewing the individual subjects it is seen that several of them did have an increased minute ventilation above the normal when at rest. However, the examination of the individual responses of B. B., H. M., and T. S. would seem to indicate that this was no serious objection, as these subjects demonstrate the principle that the response to ventilation by inhalation of carbon dioxide is not significantly related to the initial pH of the blood in these patients.

The increased resting minute ventilation, and slightly high average pH of several of the patients with emphysema, were not thought to be wholly due to hyperventilation of excitement. These patients' minute ventilations were checked on two occasions when they were told that they were not to have an arterial puncture. Under this desirable condition their minute ventilations compared favorably with those recorded on the day of the actual experiment. Those patients who had a rapid minute respiratory rate were observed in their sleep to confirm the fact that it was not due to experimental excitement. Several of the patients went back to their rooms after the experiment and slept. It was possible to obtain venous blood on three patients as they slept. The pH of this venous blood was in the order of 0.03 to 0.04 lower than the arterial sample drawn from one to two hours before.

It is well to point out that the patients were ventilating at rest near their capacities, but carbon dioxide inhalations were always discontinued before their maximal capacities were reached, for it is obvious that these patients could not respond further to carbon dioxide inhalations once their maximum was reached. Therefore, the sensitivity of the respiratory center in these patients was tested within the physical capabilities of the patients. It seems clear, therefore, that the respiratory center, while apparently less sensitive to carbon dioxide, is actually more sensitive in emphysematous patients. However, the mechanism of this phenomenon remains obscure.

SUMMARY

Quantitative studies on the response of the ventilation to carbon dioxide inhalation were carried out on twelve normal subjects, twelve patients with emphysema, and one patient with fibrosis of the lung (Boeck's sarcoid). Tidal air, respiratory rate, minute ventilation, arterial serum carbon dioxide, and pH determinations were made before and during hyperpnea produced by addition of carbon dioxide to the spirometer. Minute liter ventilation increase, divided by the millimeter increase in tension of carbon dioxide of the normal group, showed an average increase of 2.71 liters per minute for each millimeter of mercury increase of carbon dioxide, or a median value of 1.6 liters. In terms of pH this was shown to be an increase of 3.16 liters per minute for each 0.01 decrease in pH, or a median value of 2.5 liters.

The patients with emphysema were shown to have an average of 3.0 volumes per cent (7.0 per cent) more total carbon dioxide content than did the normal subjects. The average response was 1.85 liters per minute increase in ventilation for each millimeter increase in carbon dioxide tension (66 per cent that of the normal group) when both groups are considered as a whole. There was a wide variation in the response within each group and considerable overlapping between the response of the two groups existed. A statistical analysis would seem to indicate that the difference was not significant. However, the patients with emphysema did not get as much tidal exchange for a given amount of respiratory effort as did the normal subjects, and were shown by the

relationship $\frac{\textit{ventilation (in liters per minute)}}{\textit{vital capacity (in liters)}}$ to have an increased resting respiratory effort as well as a greater increment of respiratory effort for a given change in pH consequent to carbon dioxide inhalation.

From the evidence presented, it seems apparent that in terms of respiratory effort, the emphysematous patient is actually more sensitive to carbon dioxide inhalation than the normal individual. The explanation for this phenomenon is unknown at the present time.

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INTRACAVITY AND ESOPHAGEAL POTENTIALS IN RIGHT VENTRICULAR HYPERTROPHY

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RECENT investigations on intracavity potentials of the human right heart have proved of great interest in the interpretation of certain aspects of clinical electrocardiography. The initial publication of Lenègre and Maurice[1] in 1945, and subsequently that of Hecht[2] in 1946, were soon followed by two valuable contributions[3,4] to this subject presented at the Inter-American Congress of Cardiology held in Mexico City in October, 1946.

Intracardiac leads in dogs had previously been studied by Wilson and co-workers,[5,6] who were able to demonstrate the presence of an initial positive deflection, attributed to septal activation, in the right ventricular cavity of the normally activated heart. In the presence of left bundle branch block, negative deflections (QS) were found in the right ventricular cavity and diphasic complexes of the RS type, in the left intraventricular lead. In right bundle branch block, negative complexes were found in the left ventricular cavity, whereas initially positive deflections were present in the right ventricle. These studies have contributed to a more comprehensive interpretation of the human electrocardiogram.

The experimental investigations of Sodi-Pallares[7] with the exploring electrode in the cavity of the left ventricle have demonstrated an elevation of the RS-T segment due to subendocardial current of injury with a corresponding depression in precordial leads similar to that observed in recent posterior infarction. An experimental study on RS-T displacement, including intracavity potentials, has been reported by Wolferth and co-workers.[8] A comparative study of the intracavity potentials in man and dog has recently been published by Sodi-Pallares and associates.[4] These authors have made a valuable contribution to our present knowledge of this subject. Battro and Bidoggia,[3] reporting their observations on the human endocardiogram in twenty-three cases, have emphasized the similarity in configuration of the ventricular complexes obtained by introduction of the exploring electrode in the right atrial cavity (Type II) with that of the esophageal lead at the auricular level.

Our first studies on intracavity potentials were undertaken in an attempt to investigate an atypical aspect of the precordial electrocardiogram in certain cases of right ventricular hypertrophy found in chronic cor pulmonlae.[9] These

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investigations aroused our interest in the interpretation of cardiac intracavity potentials and resulted in a more detailed study with the selection of five cases of marked right ventricular hypertrophy, including three patients with chronic cor pulmonale, of which one was associated with interventricular septal defect, one patient with long-standing mitral stenosis, and one with the tetralogy of Fallot. In addition to standard, precordial, and unipolar limb leads, the esophageal electrocardiogram was recorded in all instances at auricular and ventricular levels, as well as right intracavity potentials. The present report concerns the comparative study and detailed analysis of the configuration of the QRS complexes in esophageal and intracavity leads, as well as in the unipolar lead of the right arm.

METHOD

All patients received 0.20 Gm. of sodium amytal on the eve of the procedure followed by a similar dose one hour before catheterization. The exploring electrode was introduced through the right external jugular vein, after local infiltration with Novocain. Our electrode was of the same type as that used at the Institute of Cardiology of Mexico and consisted of a catheter containing a wire connected to a small metal tip at one end (exploring electrode) and to a metal clip at the other. Unipolar leads were taken in all cases, using Wilson's central terminal. The catheter was introduced under fluoroscopic control and films were taken at the various positions in which the electrocardiogram was recorded. All patients showed an excellent tolerance to the procedure, with the exception of one to whom it was necessary to give 0.01 Gm. of morphine subcutaneously. Thirty thousand units of penicillin were administered prophylactically every three hours for forty-eight hours following the procedure. No ill effects such as fever, venous thrombosis, or other complications were observed in a one-month follow-up.

Fig. 1.—Case 1. W. R., a 26-year-old patient with tetralogy of Fallot. The electrocardiogram shows marked right ventricular and auricular hypertrophy.

REPORT OF CASES

Case 1.—W. R., a 26-year-old white man, had been cyanotic since birth because of congenital heart disease which had been diagnosed as tetralogy of Fallot. The electrocardiogram (Fig. 1) revealed left axis deviation of the P wave, with tall, peaked auricular complexes in Lead I, as well as in the precordial leads; marked right axis deviation of the QRS complex, with late R waves of high voltage in Lead V_1; S waves in V_5, and inverted T waves in Leads II, III, aV_F, and the right precordial leads. The electrocardiogram indicated marked right ventricular hypertrophy. The potential recorded with the electrode in the upper part of the right auricle (Fig. 2,*A*) revealed deep, negative P waves with slight variations in certain complexes which showed a small initial positive deflection (P_{QS} and P_{RS})* and marked elevation of the P-R segment. The ventricular complexes were essentially positive, being preceded by a small Q wave (qR); the T waves

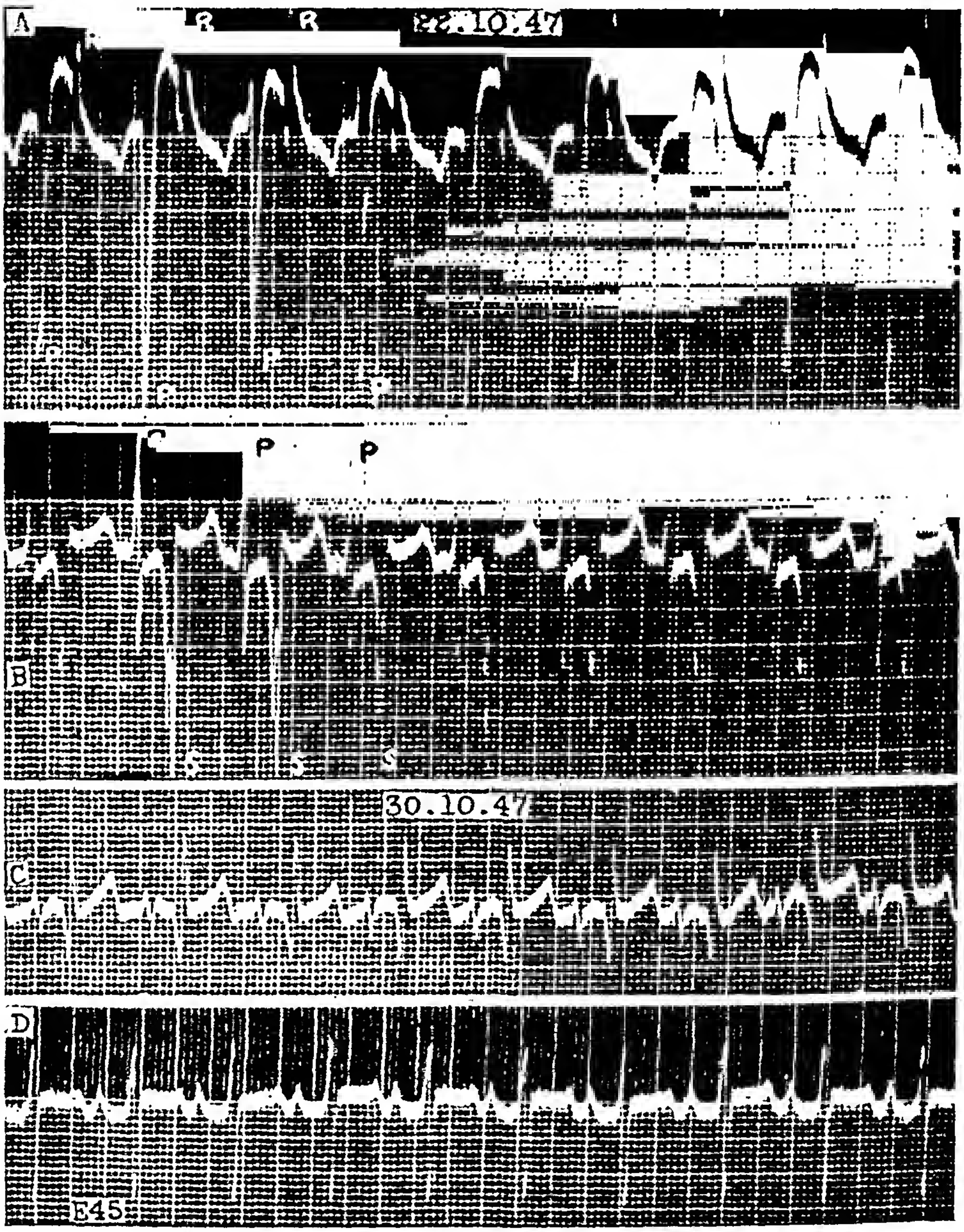

Fig. 2.—Case 1. W. R. *A*, Intracavity potential of the right auricle; *B*, right intraventricular lead; *C*, esophageal lead at auricular level; *D*, esophageal lead at ventricular level.

*According to Hecht's[2] terminology which is followed in this paper.

were inverted. In leads from the right ventricular cavity (Fig. 2,*B*), the auricular deflection was diphasic (P_{RS}) and the QRS complex was notched and essentially negative. The RS-T segment showed positive displacement and the T waves were upright. The esophageal lead at the auricular level, E40 (Fig. 2,*C*), revealed intrinsic deflections of the P waves, ventricular complexes of the QR type, and positive T waves. At the ventricular level, E45 (Fig. 2,*D*), the P waves were positive while the QRS complexes were of the RS type with a predominant negative phase and positive T waves.

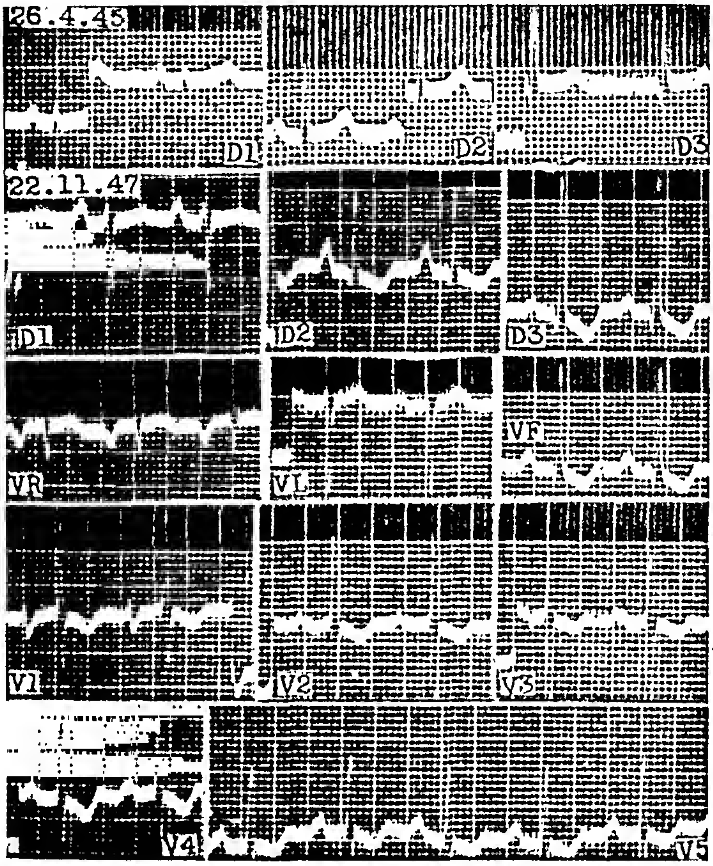

Fig. 3.—Case 2. A. P. C., a 21-year-old woman with mitral stenosis. The electrocardiogram taken on Nov. 22, 1947, shows signs of marked right ventricular and left auricular hypertrophy, in addition to digitalis effects. The previous tracing taken April 26, 1945, is not outside normal limits.

CASE 2.—A. P. C., a 21-year-old white woman, was first seen by us in 1944, with mitral stenosis, a past history of rheumatic fever, and several episodes of cardiac decompensation. The electrocardiogram taken on Nov. 22, 1947 (Fig. 3), showed marked right ventricular hypertrophy, P waves of high voltage in Leads I and II, and RST-T changes attributed to digitalis. A previous record (April 26, 1945) was not far outside normal limits. The intracavity potential registered at the midauricular level (Fig. 4,*A*) showed diphasic P waves (P_{RS}) of high voltage, slight upward displacement of the P-R segment, essentially negative ventricular complexes (rS), and upright T waves. With the catheter in the right branch of the pulmonary artery (Fig. 4,*B*) auricular deflections were of the P_{qrS} type and ventricular complexes were of the rSr′ type with a positive displacement of the RS-T segment. Esophageal potentials at various auricular levels (Fig. 4,*C*, *D*, and *E*) revealed negative P waves at the upper part of the left auricle, diphasic deflections at the midauricular position (E30), and upright P waves at the lower level (E35). The QRS

complexes corresponding to Positions E25, E30, and E35 were essentially negative (Qr) at the two upper levels and of the qR type with the electrode in the lower position. Upright P waves waves showing no evidence of intrinsic deflections, as well as positive QRS complexes, were observed at the ventricular level E40.

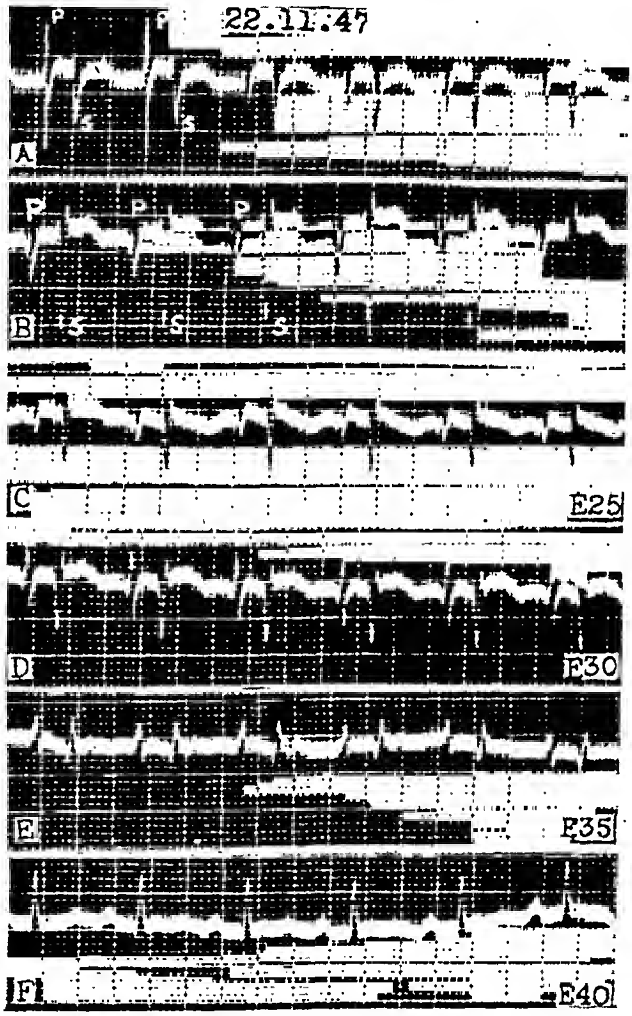

Fig. 4.—Same case as in Fig. 3. Unipolar leads from: *A*, right auricular cavity; *B*, right ventricular cavity. *C*, *D*, and *E* represent esophageal leads at three auricular levels. *F*, Esophageal lead at ventricular level.

CASE 3.*—N. A. P., a 37-year-old man with a history of chronic bronchitis since early youth, was admitted to the hospital with signs and symptoms of predominantly right heart failure of one month's duration. Roentgen examination on admission revealed marked enlargement of the right auricle and ventricle, in addition to a prominent pulmonary conus. The electrocardiogram taken on Aug. 11, 1947 (Fig. 5), showed marked right axis deviation (+150°), prominent P waves in Leads II and III, and R waves present in the unipolar right arm lead. The precordial leads were atypical,[9] with absent R waves on the right side of the precordium and S waves present in Lead V_6. Fig. 6 represents serial esophageal leads as well as the intracavity potentials. With the exploring electrode in the superior vena cava (Fig. 6,*A*), the P waves were negative, whereas the ventricular complex was essentially positive and of the rsR type with inverted T waves. With the electrode in the upper part of the right auricle (Fig. 6,*B*), the P waves were negative (P_{QS}) with upward displacement of the P-R segment, R waves of high voltage were preceded by a small initial negative deflection (qR), and the T waves were inverted. The right intraven-

*This case and the following case as well have been previously reported.[9]

tricular potential showed predominantly positive, diphasic P waves (plus-minus), deep negative ventricular complexes of the QS type, and marked elevation of the RS-T segment. The potentials obtained with the exploring electrode in the pulmonary conus and right branch of the pulmonary artery showed a similar configuration (Fig. 6,*D* and *E*). The P waves were negative; M-shaped QRS complexes with slight variations in amplitude of certain deflections and with negative T waves were observed. Esophageal leads at the auricular level (E30) are represented in Fig. 6. The auricular complexes showed an intrinsic deflection and QRS complexes of the qR type. At the ventricular level (E50), P waves were upright and showed no evidence of intrinsic deflections. The QRS complexes displayed an RS configuration and the T waves were negative.

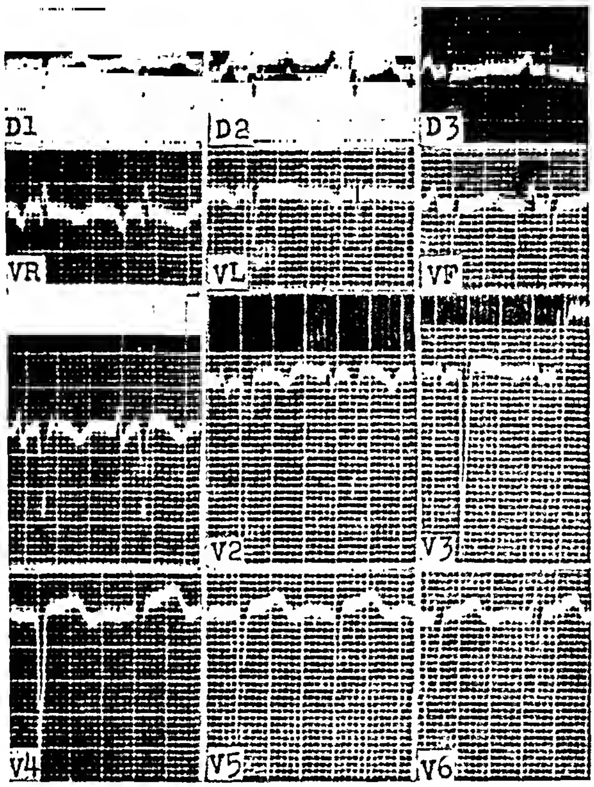

Fig. 5.—Case 3. N. A. P., a 37-year-old man with chronic cor pulmonale. Right axis deviation (+150°); "pulmonary" P waves. Absent R waves on the right side of the precordium, with S waves on the left. The electrocardiogram shows signs of right ventricular hypertrophy with atypical precordial leads.

Case 4.—J. A. A., a 54-year-old man with interventricular septal defect, had suffered with bronchial asthma since childhood. The patient had had several hospital admissions since 1943 because of right heart failure, which had improved with treatment, and paroxysms of auricular tachycardia with 2:1 A-V block. Roentgen examination revealed emphysema and moderate left ventricular hypertrophy, in addition to marked enlargement of the right auricle and ventricle. The tracing taken on Dec. 19, 1946 (Fig. 7), showed low voltage of the QRS complex with right axis deviation, prominent P waves in Leads II and III, absent R waves in Leads V_1 to V_4, and S waves in Lead V_6. This atypical precordial pattern has been described in right ventricular hypertrophy.[9] The records presented in Fig. 8 were taken during a paroxysm of auricular tachycardia with A-V block and showed prominent P waves in Lead CR_1. The intracavity potential of the upper part of the right auricle (*A*) showed deep negative P waves

(P_{QS} and P_{rS}), and ventricular QRS complexes of low voltage with an rs configuration. At the lower auricular level (Fig. 8,*B*) P waves were of the $P_{rSr'}$ type, ventricular complexes assumed an rS configuration, and T waves were negative. The right intraventricular lead (Fig. 8,*C*) was similar to the potential obtained at the lower part of the auricle. With the exploring electrode in the pulmonary conus (Fig. 8,*D*), the P waves were essentially negative and the QRS complexes were diphasic and of the RS type. Esophageal Lead E40, taken during a paroxysm of auricular tachycardia, showed positive QRS complexes, inverted T waves, and depression of the RS-T segment attributed to digitalis. It is assumed that the exploring electrode was at the ventricular level, although the shape of the P wave cannot be relied upon to determine the position of the electrode because of the ectopic rhythm.

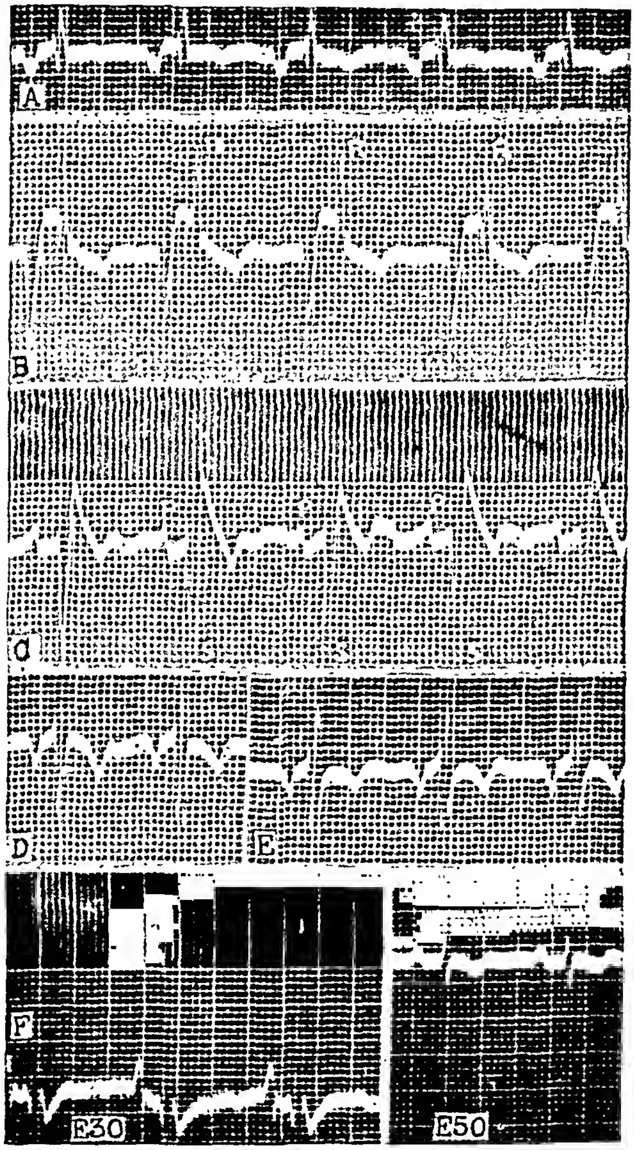

Fig. 6.—Same case as in Fig. 5. Intracavity and esophageal leads. Unipolar tracings from: *A*, superior vena cava; *B*, high auricular level; *C*, right ventricular cavity; *D*, pulmonary conus; *E*, right branch of the pulmonary artery; and *F*, esophageal leads at auricular level (*E30*) and ventricular level (*E50*).

Case 5.—I. E., a 36-year-old white woman, gave a history of bronchitis since infancy and symptoms of congestive heart failure of two months' duration. Physical examination showed an emphysematous chest, cyanosis of the extremities, and clubbing of the fingers, in addition to a

palpable liver, edema, and marked engorgement of the jugular veins. The electrocardiogram made on Oct. 16, 1947 (Fig. 9), showed a typical configuration of right ventricular hypertrophy, in addition to prominent P waves in Leads II and III. Intracavity and esophageal leads are shown in Fig. 10. The upper intra-auricular lead displayed deep negative P waves with upward displacement of the P-R segment and the QRS complexes showed R waves of high voltage preceded by a small negative deflection (qR). At the midauricular level (*B*), P waves were variable in configuration, probably because of slight changes in the position of the exploring electrode,

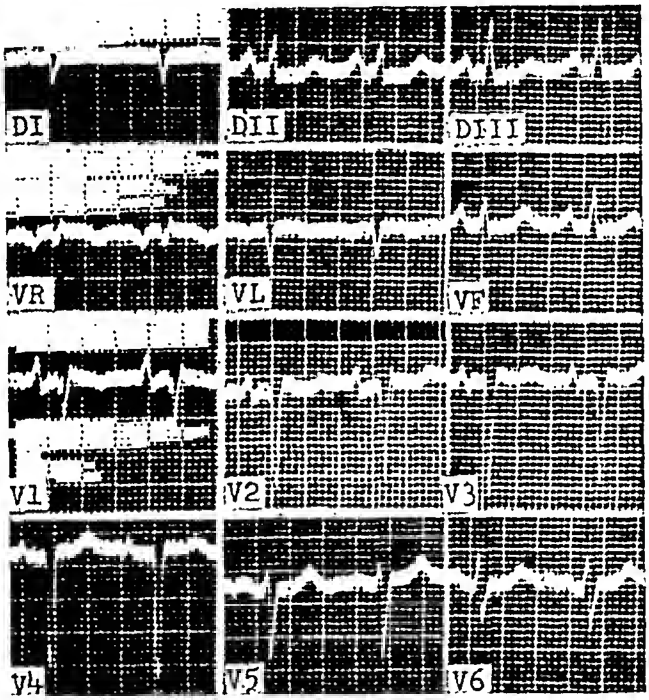

Fig. 7.—Case 4. J. A. A., a 54-year-old man with interventricular septal defect and chronic cor pulmonale. The electrocardiogram reveals right ventricular hypertrophy with atypical precordial leads.

and the QRS complexes were similar to those recorded at the higher level. The right intraventricular potential (*C*) showed positive P waves and QRS complexes of the QR type, with a deep initial negative deflection followed by an R wave. The electrocardiogram taken with the exploring electrode in the suprahepatic vein revealed negative P waves of low voltage and ventricular deflections of the qR type. The esophageal lead made at a high auricular level (E25) revealed W-shaped P waves, QRS complexes of the rSR type, and upright T waves. At a lower auricular level (E30) prominent positive P waves were observed and the ventricular complexes showed a qR configuration. At the ventricular level (E40), P waves were positive and QRS complexes were diphasic (rS) with inverted T waves.

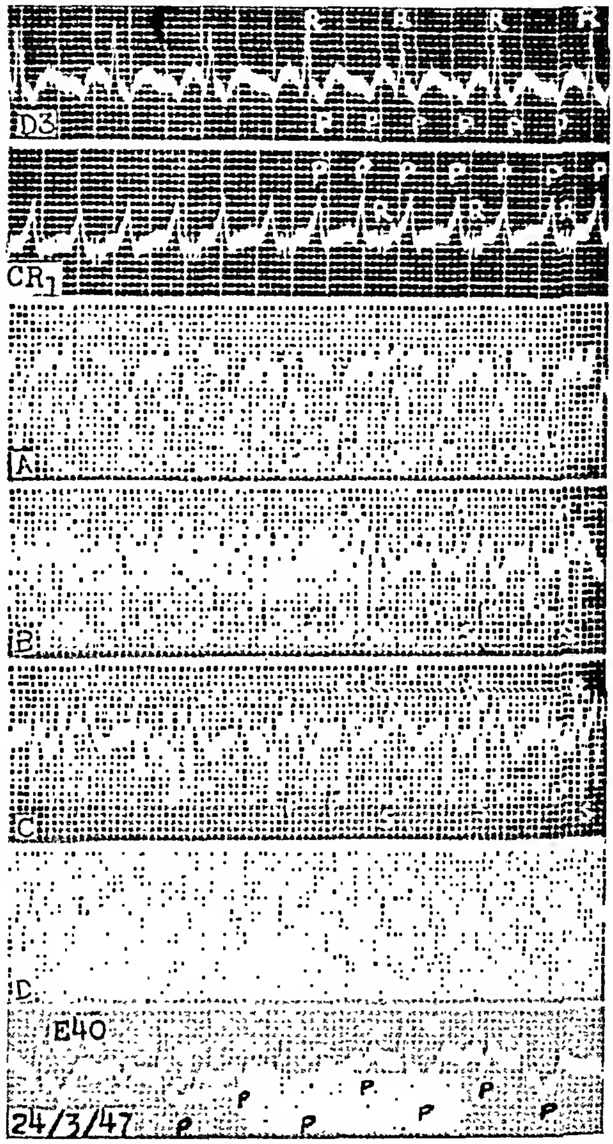

Fig. 8.—Same case as in Fig. 7. Tracings taken during paroxysmal supraventricular tachycardia with 2:1 A-V block. *A*, Intra-auricular lead at high level; *B*, low auricular level; *C*, right intraventricular potential; *D*, intraventricular lead at the pulmonary conus.

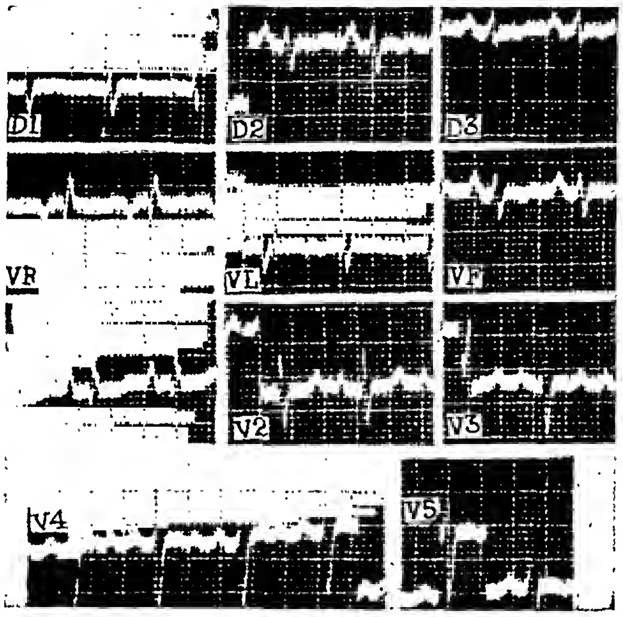

Fig. 9.—Case 5. I. E., a 36-year-old woman with chronic cor pulmonale. The electrocardiogram shows right ventricular hypertrophy with "pulmonary" P waves.

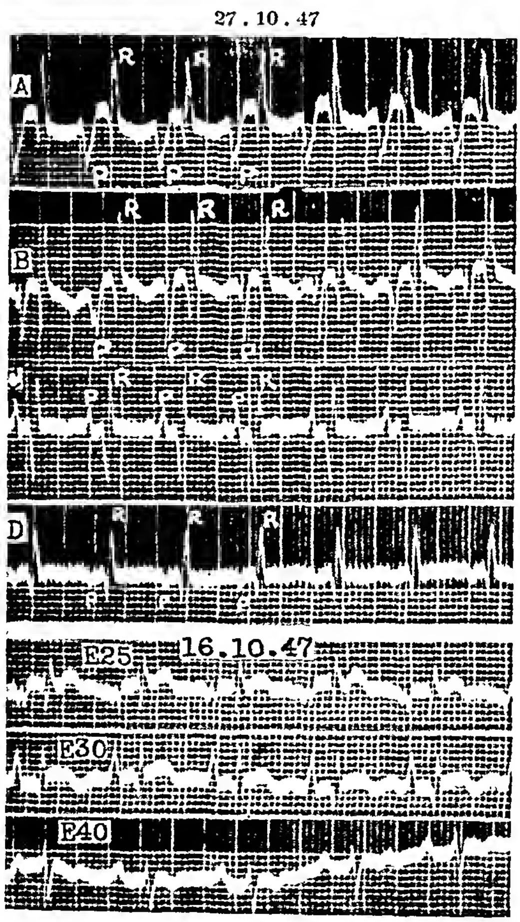

Fig. 10.—Same case as in Fig. 9. Intracavity leads taken from: *A*, high auricular level; *B*, mid-auricular level; *C*, right ventricular cavity; *D*, suprahepatic vein. The three lower tracings represent esophageal leads.

DISCUSSION

The study of intracavity potentials has contributed to a better understanding of the fundamental concepts of electrocardiography. To some extent this has been accomplished by theoretical consideration and to some extent by experimental evidence.

A comparative study of intracardiac leads in man and the dog has recently been carried out by Sodi-Pallares and his associates.[4] These authors, as well as Battro and Bidoggia,[3] have described the configuration of intracavity tracings in normal individuals. The shape of the P waves and QRS complexes is subject to great variation, according to the position of the exploring electrode at different levels. Thus, P waves are essentially negative (P_{QS}) in the upper part of the right auricle near the sinus node and in the superior vena cava. At midauricular levels, the P waves are diphasic, and at lower levels the auricular complexes assume an essentially positive configuration (P_{RS}). The tracings obtained with the electrode in the right ventricular cavity show positive P waves of low voltage. The ventricular complexes recorded in the intra-auricular leads are always predominantly negative; they are of the Qr and Qrs type at upper and midauricular levels and usually of the rSr′ and rS type at lower levels. In cases of right bundle branch block and right ventricular hypertrophy, intra-auricular tracings reveal an increase in voltage of the late R wave (Qr, Qrs, or rSr′). It has been assumed that this deflection represents the late activation of certain portions of the right ventricle.[4] The QRS complexes obtained with the electrode in the right ventricular cavity are usually of the rS type. The initial positive deflection (r) has been attributed by Sodi-Pallares[4] to septal activation. Table I represents a summary of the configuration of auricular and ventricular deflections in intracavity and esophageal leads obtained in a study of five cases of marked right ventricular hypertrophy.

Auricular Complex.—The shape of the P wave in tracings made at the various intra-auricular levels was similar to the normal, although of higher voltage in Cases 1 and 3. Slight changes in the configuration of the P wave were occasionally observed in successive auricular complexes and attributed to variations in the position of the exploring electrode (Figs. 2,*A* and 8,*A*). In Cases 3, 4, and 5 (Figs. 6,*B*, 8,*A*, and 10,*A*), the auricular complexes were slurred and notched. In Case 4 essentially negative P waves ($P_rS_{r'}$) were present at low auricular levels (Fig. 8,*B*), as opposed to the positive deflections which are usually observed at these levels. This unusual finding was probably due to the presence of an ectopic rhythm (paroxysmal auricular tachycardia). A similar explanation may be offered in the same case for the presence of predominantly negative P waves in the leads from the right ventricular cavity, since in all other patients tracings made at this level showed upright P waves, such as are observed in normal tracings. With the exploring electrode in the pulmonary conus and in the right branch of the pulmonary artery (Figs. 4,*B* and 6,*E*), essentially negative P waves were obtained. This configuration is probably due to the direction of the wave of excitation, which is such that the wave is away from the exploring electrode when it is situated at these points. The same configuration

also was observed when the electrode was placed in the superior vena cava (Fig. 6,*A*). Negative P waves were found when the electrode was placed in the suprahepatic vein, which is situated at a lower level but far to the right of the sinus pacemaker. With the exception of Case 4, all patients showed an elevation of the P-R segment at auricular levels, possibly because of contact of the exploring electrode with the endocardial surface of the right atrium.

Ventricular Complexes.—The QRS complexes obtained by placing the electrode in the right auricular cavity were essentially positive in three patients (Cases 1, 3, and 4). These complexes displayed a similar configuration to that described by Sodi-Pallares[4] in right ventricular hypertrophy. However, in the remaining two patients (Cases 2 and 5) this was not observed, since predominantly negative deflections were recorded in the intra-auricular lead (Figs. 4,*A*, 8,*A*, and 8,*B*). In leads obtained from within the right ventricular cavity, only one patient (Fig. 8,*C*) showed an initial positive deflection ascribed to septal activation. This deflection was also present and of higher voltage in the region of the pulmonary conus (Fig. 8,*D*). All other patients displayed initial negativity of the QRS complexes (QS and QR) in the intraventricular lead. The potential of the pulmonary conus showed an initial positive deflection in Cases 3 and 4. In Case 4 an early R wave (r) was also found in the right ventricular cavity, whereas in Case 2 this deflection was present only in leads obtained from the region of the pulmonary conus. With the electrode in the right branch of the pulmonary artery, Cases 2 and 3 showed predominantly negative QRS complexes with a small initial R wave (r). The configuration of the ventricular complex in leads from the superior vena cava was of the rsR′ type in Case 3 and the configuration in leads from the suprahepatic vein was of the qR type in Case 5. In Cases 1, 3, and 5, upward displacement of the RS-T segment was observed in the right ventricular cavity leads. This may be attributed to subendocardial current of injury caused by contact of the exploring electrode with the inner surface of the right ventricle.

Esophageal Leads.—The esophageal leads taken in these patients were of interest and yielded certain data which deserve to be analyzed in this study. Thus, we were able to confirm the observations of Battro and Bidoggia[3] regarding the similarity in configuration of the QRS complexes in right intra-auricular leads to that of the esophageal potentials at auricular levels. This similarity was noted in all of our patients, particularly in Cases 1 and 3, as can be seen in Fig. 2 (compare the QRS complex in *A* and *C*) and Fig. 6 (compare *B* and *E30*). Occasional differences in amplitude were observed (Fig. 6). As we have previously mentioned, predominantly positive QRS complexes were found by Sodi-Pallares[4] in the right intra-auricular lead in cases of right ventricular hypertrophy. This was observed in three of our patients (Cases 1, 3, and 5), in all of whom the esophageal leads obtained at auricular levels revealed QRS complexes of a similar configuration. In the remaining two patients (Cases 2 and 4) the intra-auricular and esophageal leads were comparable, and did not show the predominance of positive deflections described by Sodi-Pallares. On the basis of these findings we were able to establish a certain correlation between the

TABLE I. CONFIGURATION AND COMPARATIVE STUDY OF INTRACAVITY AND ESOPHAGEAL POTENTIALS IN FIVE PATIENTS WITH RIGHT VENTRICULAR HYPERTROPHY

POSITION OF EXPLORING ELECTRODES		DIAGNOSIS				
		CASE 1 (W. R.)	CASE 2 (A. P. C.)	CASE 3 (N. A. P.)	CASE 4 (J. A. A.)	CASE 5 (I. E.)
		TETRALOGY OF FALLOT	MITRAL STENOSIS	CHRONIC COR PULMONALE	CHRONIC COR PULMONALE PLUS INTERVENTRICULAR SEPTAL DEFECT	CHRONIC COR PULMONALE
High intra-auricular lead	P	Pqs and PrS (deep)	—	Pqs (deep, notched)	Pqs and PrS (notched)	Pqs (slurred)
	PR	Upward displacement	—	Upward displacement		Upward displacement
	QRS	qR (tall R)	—	qR	rs (low voltage)	qR (tall R)
	T	Negative	—	Negative	Upright.	Negative
Mid-auricular lead	P	—	Prs	—	—	PqrS and Pqs
	PR	—	Upward displacement	—	—	Upward displacement
	QRS	—	rS	—	—	qR
	T	—	Upright	—	—	Negative
Low auricular lead	P				PrSr′	
	PR				—	
	QRS				rS —	
Intraventricular lead	P	Prs (high voltage)		Prs	PrSr′	Pr
	QRS	QS (deep)		QS (deep)	rS	QR
	ST	Upward displacement		Upward displacement	—	Upward displacement
	T	Upright		Diphasic (?)	—	Negative

Pulmonary conus	P QRS ST T			Pqs rSr′S′ Negative	PrSr′ RS	
Right branch of pulmonary artery	P QRS T		PqrS rSr Upright	Pqs rSr′S′ Negative		
Superior vena cava	P QRS T			Pqs rsR′ Negative		
Suprahepatic vein	P QRS T					Pqs qR Flat
Esophageal lead at high auricular level	P QRS T	Prs QR Upright	Pqrs rSr′ Diphasic			Pqrs rSR′ Upright
Esophageal lead at midauricular level	P QRS T		Prs Qr Upright			
Esophageal lead at low auricular level	P QRS T		Prs qR Flat	Prs qR (high voltage) Flat	Pqs R Negative	Pr qR Upright
Esophageal lead at ventricular level	P QRS T	Pr RS Upright	PR R Upright	Pr RS Negative	Pr R Negative	Pr rS Negative

QRS complexes in right intra-auricular leads and in esophageal leads obtained at the auricular level in cases of right ventricular hypertrophy. These findings confirm the views of Battro and Bidoggia[3] in normal individuals.

Comparative Study of Lead aV_R With Esophageal and Intracavity Potentials: The unipolar lead of the right arm is normally characterized by essentially negative deflections, as a result of the transmission of the negativity of the ventricular cavities through the valvular orifices at the base of the heart, to the right shoulder and right arm. However, the potential variations of this extremity do not correspond exclusively to cavity potentials, but most likely represent an association of the latter with potential variations of other regions, particularly those of the free wall of the right ventricle. It may be difficult at times to determine the relative contribution of each one of these potentials to the configuration of Lead aV_R. In cases of right ventricular hypertrophy and right bundle branch block, ventricular complexes of the QR or qR type are usually observed in this lead. The R waves are due either to late activation of certain portions of the right ventricle (hypertrophy) or to late activation of the epicardial surface (bundle branch block). A definite similarity in the configuration of QRS complexes was observed in the comparative study of Lead aV_R with auricular esophageal and right intra-auricular potentials. In Cases 1, 3, and 5, a positive deflection preceded by a Q wave was present in Lead aV_R and was also found in the esophageal and intra-auricular leads (Figs. 1, 5, and 9, compared with Figs. 2, 6, and 10). In Cases 2 and 4, Lead aV_R showed small R waves (r) with a similar configuration in esophageal and intra-auricular leads (Figs. 3 and 7, compared with Figs. 4 and 8, respectively). Since in cases of right ventricular hypertrophy the QRS complex in the intra-auricular lead is essentially positive, it is evident that this configuration is not due exclusively to the transmission of the intraventricular potential which is predominantly negative (with the exception of Case 5, Fig. 10, in which a QR type of deflection was recorded in the right ventricular cavity). Thus, it seems likely that the positive deflection obtained in the intra-auricular lead, as well as in Lead aV_R, and in the esophageal lead at the auricular level, is due to the late activation of certain portions of the free wall of the enlarged right ventricle.

SUMMARY

Intracavity potentials obtained by heart catheterization were studied in five patients with right ventricular hypertrophy, including three patients with chronic cor pulmonale (one associated with interventricular septal defect), one patient with mitral stenosis, and one with the tetralogy of Fallot. Esophageal leads, as well as standard, precordial, and unipolar limb leads, were taken in all patients. A comparative study of the esophageal leads made at auricular levels, intra-auricular potentials, and Lead aV_R revealed a definite similarity in the configuration of the QRS complexes.

A preponderance of positive deflections in the intra-auricular lead was observed in three patients, whereas essentially negative deflections were noted in two patients, in both of whom there was similarity in the configuration of the

esophageal auricular lead and the unipolar lead of the right arm. The intracavity potential of the right ventricle revealed a tall R wave preceded by a deep negative deflection (QR) only in one patient. An explanation for this finding has not been attempted. In the remaining four patients, the intraventricular lead revealed essentially negative QRS complexes. Thus, in these patients the tall R waves found in the intra-auricular lead do not represent the potential variations of the right ventricular cavity, and are probably due to the late activation of certain portions of the free wall of the enlarged right ventricle.

We are deeply indebted to Dr. J. Bergstein, Department of Radiology, and to Dr. Humberto Barreto, Department of Surgery, for their invaluable cooperation and assistance in the present study.

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THE ELECTROCARDIOGRAM IN FAMILIAL PERIODIC PARALYSIS

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FAMILIAL periodic paralysis is a rare disease which was described by Cavare in 1853. The disease is characterized by recurrent attacks of quadriplegia which usually occur at night and are associated with a low level of serum potassium. The administration of potassium salts hastens recovery from the attack. The clinical aspects of the cases to be reported form the material of a separate communication. It is our purpose here to report the electrocardiographic findings in two cases of familial periodic paralysis, to discuss their diagnostic value, and to consider the significance of high and low levels of serum potassium in certain abnormal clinical states.

Observations concerning the role of hyperpotassemia will be considered first. Keith, Burchell, and Bagenstoss[1] observed that high levels of serum potassium were associated with characteristic electrocardiographic changes, and stated, "Among normal persons, induced mild hyperpotassemia causes increased height of the T waves, and the degree of increase (of serum potassium) correlates well with the height of the T waves." Frequently this change is quite distinctive in that the base of the T wave becomes narrower than normal, and the apex sharp or peaked. With greater increases in the serum potassium level, partial A-V block and intraventricular block may develop. Rather similar findings were obtained in dogs by Winkler, Hoff, and Smith.[2] Following the intravenous injection of potassium chloride in isotonic solution, a marked increase in the height of the T wave was noted as the first electrocardiographic change; with progressive hyperpotassemia, depression of the RS-T segment, later intraventricular block, still later disappearance of P waves, and finally cardiac arrest occurred. Sharpey-Schafer[3] showed a rise of the T wave following the administration of potassium in cases of myxedema. In these patients the potassium levels were normal and there was no relationship implied between the effect of potassium and the similar effect of thyroid hormone in elevating the T waves. In renal insufficiency high levels of serum potassium may be present. Keith and his co-workers[1] reported electrocardiographic observations in three such instances and noted particularly the development of intraventricu-

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lar block, later prolonged A-V conduction time, and finally disappearance of the T waves. They drew a close comparison of their results with those of Winkler, Hoff, and Smith.[2] Observing no uniform increase in the height of the T wave, they attributed this lack to the presence of uremic pericarditis. It is clear, then, that the effects of hyperpotassemia on the electrocardiogram are prolongation of the A-V conduction time, intraventricular block, and depression of the RS-T segment. The T wave is increased in height and peaked, though it may be low or inverted in association with uremic pericarditis.

A low level of serum potassium, on the other hand, has been correlated with electrocardiographic changes in familial periodic paralysis, diabetic acidosis, chronic nephritis, and in overactivity of the adrenal cortex. Stewart, Smith, and Milhorat[1] were the first to report a case of familial periodic paralysis in which serial tracings taken during an attack were correlated with serum potassium levels. They reported prolongation of the P-R interval, intraventricular block, prolongation of the Q-T interval, alteration in the form of RS-T segments, and a decrease in the amplitude of the T waves. It should be pointed out that certain findings, namely, increase in the P-R interval and prolongation of intraventricular conduction, are common to both high and low serum potassium levels, whereas the height of the T wave is elevated in hyperpotassemia and depressed in hypopotassemia. Stoll and Nisnewitz[5] reported a marked increase in the A-V conduction time and a flattening of the T wave during an attack in a case of familial periodic paralysis. They demonstrated that the conduction defect returned to normal upon recovery, and believed that there was increased vagal tone during the attack. Brown and his associates[6] have reported three cases of muscular paralysis of the sporadic type, associated with low serum potassium levels, in which there was increased excretion of urinary potassium secondary to renal disease. Two of these cases were defined as chronic nephritis. In each instance there was a low to isoelectric T wave during the attack, with a slight depression of the RS-T segment. In one case there was a partial A-V block with an associated Wenckebach phenomenon. In one case the Q-T interval was found to be prolonged. Martin and Wartman[9] have recently completed an excellent study of the electrolyte pattern of diabetic acidosis in relationship to electrocardiographic changes. They observed a high degree of correlation between low T waves and low serum potassium levels, but were unable to see a relationship between low levels of serum potassium and prolonged Q-T intervals. They particularly emphasized the very low serum potassium in diabetic acidosis as the most striking of the electrolyte changes noted, but were unwilling to attribute the abnormal electrocardiographic pattern to any specific electrolyte. Holler[7] reported a very unusual case of diabetic acidosis in which diaphragmatic paralysis developed. During the attack a serum potassium level of 9.8 mg. per cent was recorded. An electrocardiogram obtained before the administration of potassium chloride disclosed inversion of P_2 and P_3 and depression and sagging of the RS-T segment with low T waves in Leads I, II, and III. An electrocardiogram taken five days later showed no abnormalities. McQuarrie[10] pointed out the association of unusually low serum potassium with low to isoelectric T waves and overactivity of the adrenal cor-

tex. In states accompanied by low serum potassium, A-V block and depression of the RS-T segments appear just as in hyperpotassemia, but in contrast, the T waves are low and the Q-T interval is usually prolonged.

CASE STUDIES

In the following two cases of familial periodic paralysis, electrocardiographic findings are correlated with the level of serum potassium.

CASE 1.—W. W., a 25-year-old white man, was admitted to the Cedars of Lebanon Hospital on Feb. 6, 1941, during an attack of familial periodic paralysis. Electrocardiographic tracings were obtained on this day (Fig. 1). The RS-T segment in Lead I showed a moderate degree of sagging and the RS-T take-off in Leads II and III was depressed. In Lead CF_4 the RS-T take-off was depressed and there was marked sagging of the RS-T segment. The Q-T interval was found to be 0.6 second, which, with a heart rate of 75 per minute, indicated marked prolongation. A serum potassium level done on Feb. 7, 1941, at 10:45 A.M. was 13 mg. per 100 cubic centimeters. A tracing taken on Feb. 8, 1941, showed a return to normal, the Q-T interval measuring 0.4 at at a rate of 60 beats per minute. The T wave was elevated and the base narrowed, as compared with the previous tracing. A serum potassium level done on this day was 26.2 mg. per 100 cubic centimeters.

Six years later the patient was admitted to the Los Angeles County General Hospital on the night of Sept. 13, 1947, following an altercation, as a result of which he sustained an injury to his left eye. On Sept. 14, 1947, the patient underwent surgery under nitrous oxide and intravenous sodium pentothal anesthesia, following which he developed an attack of quadriplegia which had its onset at about 7:00 P.M. that night. The attack persisted until Sept. 16, 1947. A blood specimen taken on the evening of Sept. 14, 1947, disclosed the serum potassium, as done by the chloroplatinate method of Tenery and Anderson,[8] to be 11.1 mg. per 100 cubic centimeters.* The reported level in this particular specimen may have been higher than the actual level, since there was a blood clot in the specimen. An electrocardiographic tracing was made on Sept. 15, 1947, at 10:00 A.M. (Fig. 2, *A*). At a heart rate of 67 per minute, the Q-T interval was found to be 0.6 second in the classical leads and 0.7 in Lead CF_4. The T waves were grossly abnormal, in that they showed a smooth, rounded contour with practically symmetrical ascending and descending limbs. The RS-T segments were depressed in all leads. The serum potassium at 11:00 A.M. was found to be 7.8 milligrams. At 3:30 P.M. the same day the blood level was found to be 6.3 milligrams. Inasmuch as the serum potassium level was considered to be dangerously low, 1.0 Gm. of potassium chloride was given intravenously immediately and 1.0 Gm. given orally four times daily. An electrocardiogram taken at 4:00 P.M. (Fig. 2, *B*) disclosed a Q-T interval of 0.6 second with a heart rate of 75 in the classical leads. There was essentially no change from the previous tracing except that a low, broad T wave was observed in Lead III and a lowering of the T wave was seen in Lead CF_4. The P waves in CF_4 were smaller and inverted. A tracing taken at 11:00 P.M. that same day (Fig. 2, *C*) did not disclose any change from the previous tracing. On Sept. 16, 1947, at 8:00 A.M. (Fig. 2, *D*) the electrocardiogram showed a decided change. At this time the patient had made marked recovery from his paralysis. The T waves were lower but showed a double positive contour. In the precordial leads the secondary peak of the T wave was very prominent. The depressed RS-T take-off was still present in Lead II, but in the other leads the RS-T take-off had returned to the isoelectric line and was slightly above the isoelectric line in Lead I. The T wave was 1.0 mm. high in Lead II in comparison with a T wave of 3.0 mm. in the tracing taken on Sept. 15, 1947, at 10:00 A.M. (Fig. 2, *A*). A blood study done at 10:20 A.M. on Sept. 16, 1947, showed the serum potassium level to be 17.2 mg. per 100 cubic centimeters. The Q-T interval was 0.4 second. An electrocardiographic tracing done at 1:00 P.M. on Sept. 16, 1947 (Fig. 2, *E*), showed the Q-T interval to be 0.36 second with a heart rate of 75 per minute. The tracing now

*Blood chemistry data furnished by Dr. Helen Martin.

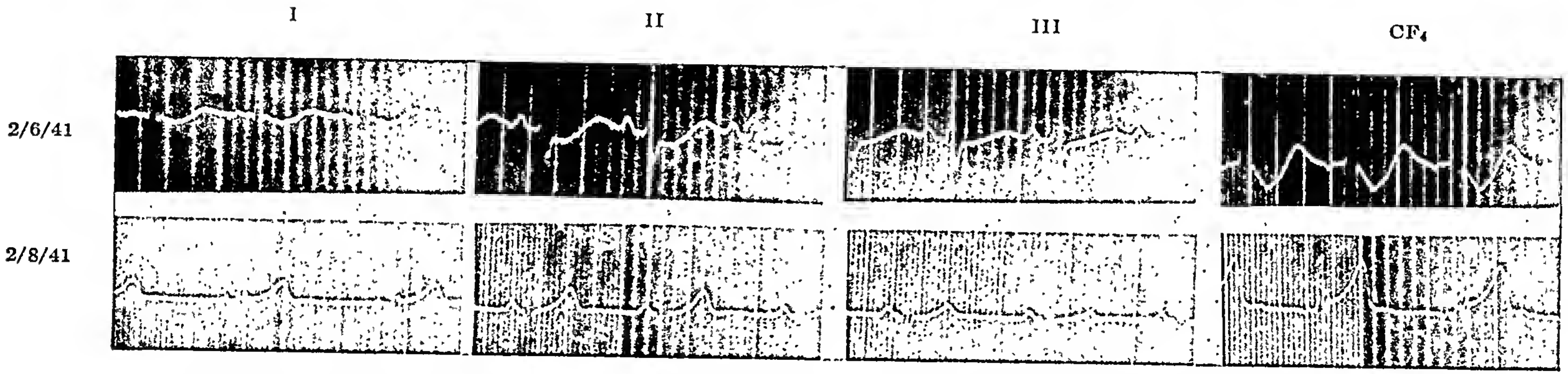

Fig. 1.—Tracings taken on Feb. 6 and Feb. 8, 1941, respectively. In the first tracing the RS-T segment in Lead I is sagging and the RS-T segment in Lead II is depressed, with a Q-T interval of 0.60 second. The second tracing shows a return to normal with a normal Q-T interval of 0.40 second.

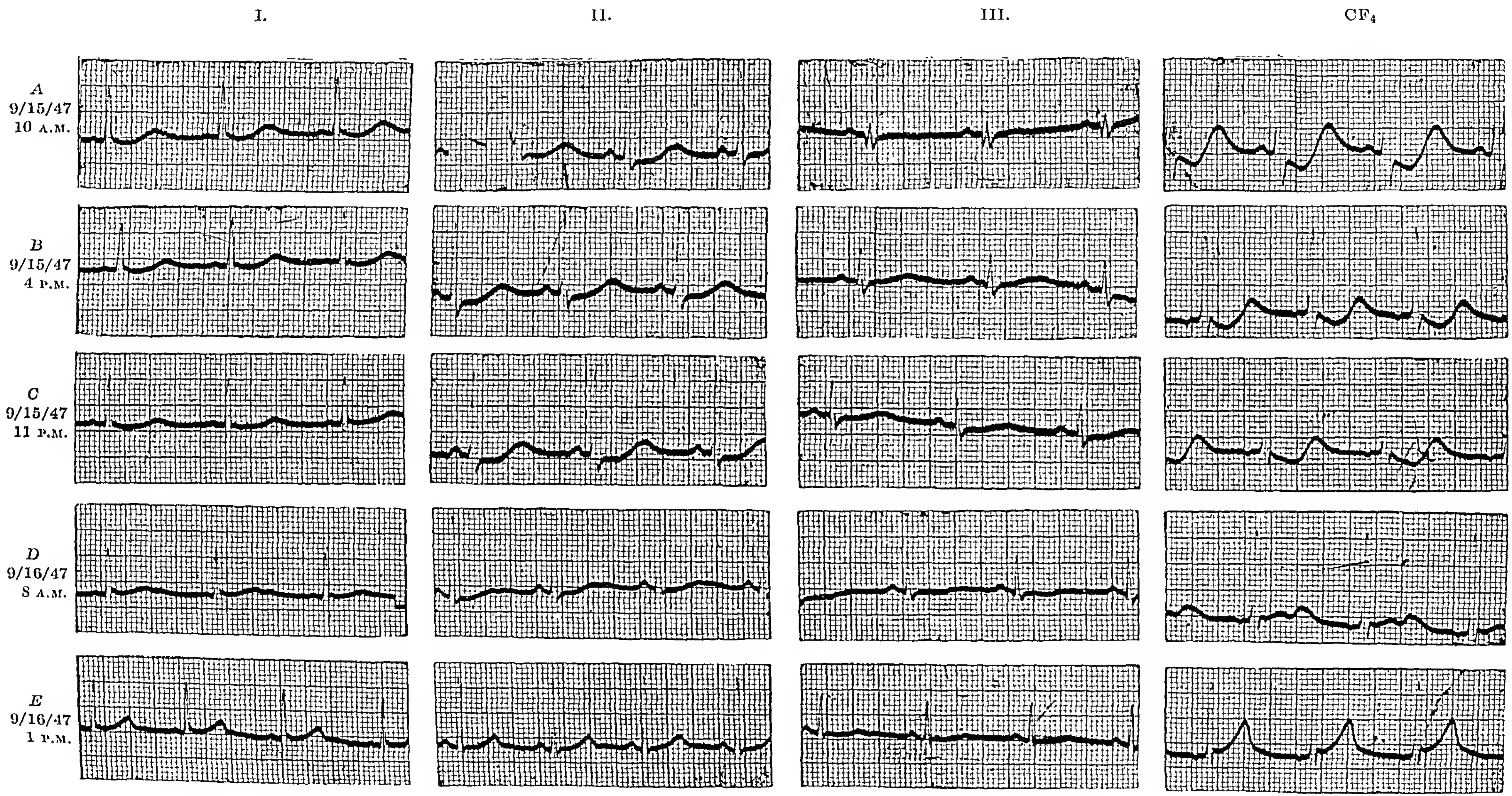

Fig. 2.—Serial tracings taken during a single attack. *A*, T waves have a rounded contour with symmetrical limbs. The RS-T segments in all leads are depressed. *B*, The T waves in CF_4 are lower and the Q-T interval is now 0.64 second. *C*, No essential changes from *B*. *D*, T waves are no lower and have a double positive contour in CF_4. *E*, Tracing is now within normal limits.

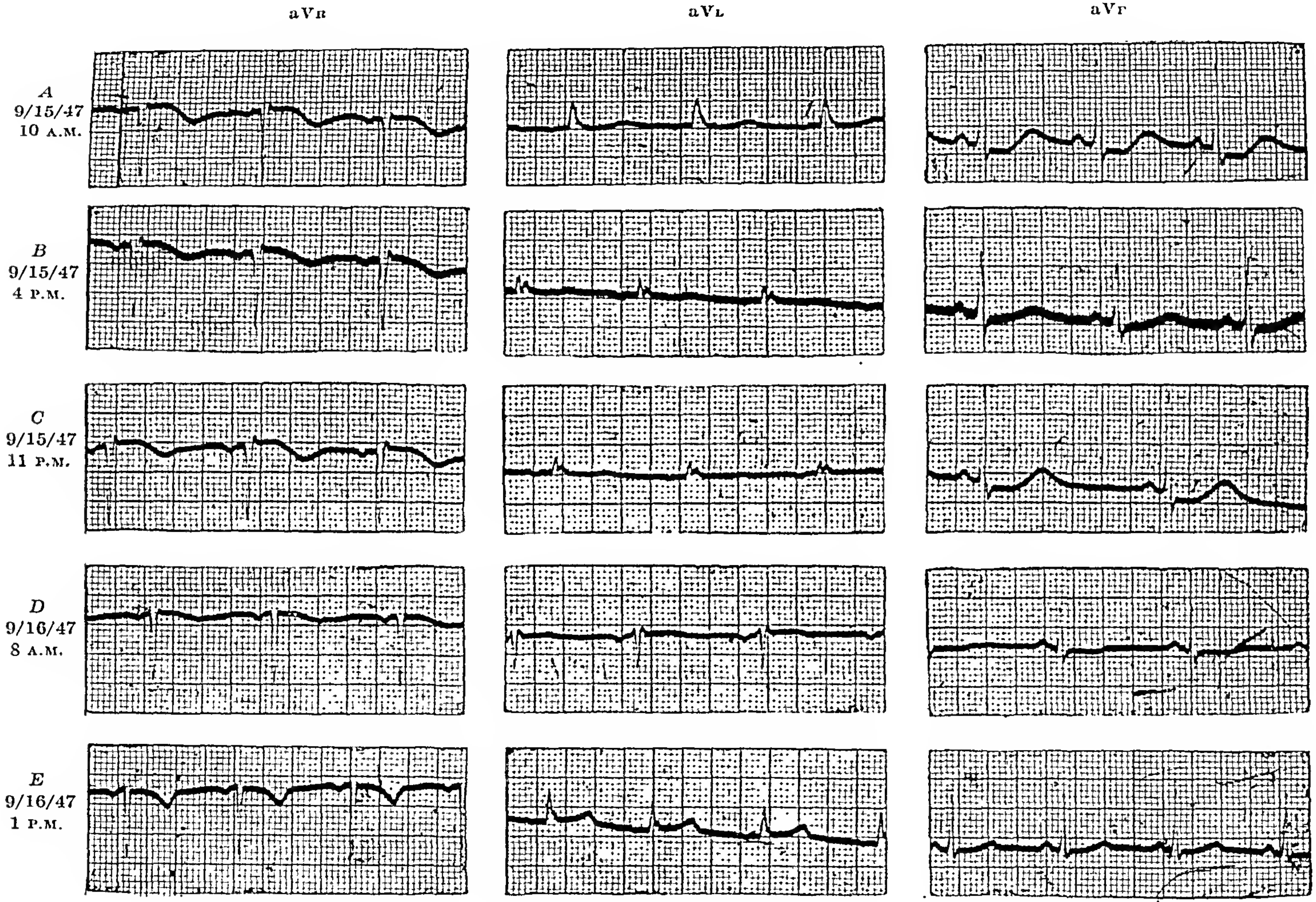

Fig. 3.—Serial tracings using unipolar leads. *A*, Marked prolongation of the Q-T interval (0.63 second) in aV_R and aV_F. *B*, The Q-T interval has shortened to 0.40 second in six hours. The T waves have increased in height between *A* and *E*, a period of twenty-seven hours. The RS-T segment, which is depressed in Lead aV_F of *A*, has returned gradually to the base line in *E*.

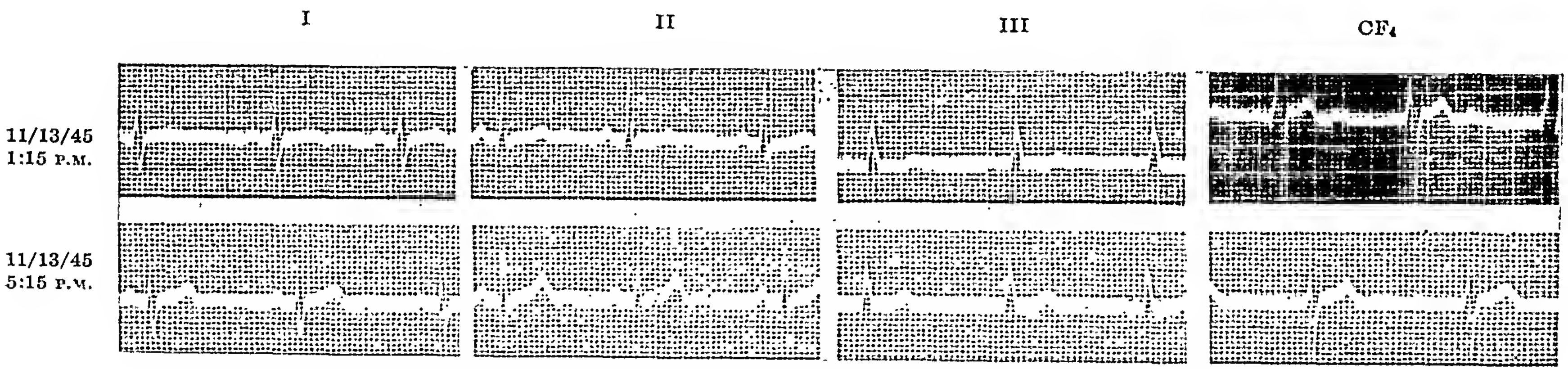

Fig. 4.—Tracings taken in terminal phase of paralysis in Case 2. Low T waves and prominent U waves are seen in the first tracing. In the second tracing T waves have become more prominent and U waves are barely discernible.

appeared to be within the normal range; the RS-T segments were no longer depressed and the RS-T take-off in the precordial leads was normally elevated. The T waves showed long ascending and short, sharp descending limbs and were normally peaked. Unipolar limb leads taken at these times (Fig. 3) showed comparable RS-T segment changes and the same dramatic alteration in the contour of the T waves.

Case 2.—R. S., a 15-year-old white boy, was admitted to the Santa Fe Hospital during an attack of familial periodic paralysis. A serum potassium determined on the day of admission was 18.2 mg. per 100 cubic centimeters. An electrocardiographic tracing (Fig. 4) taken on Nov. 13, 1945, at 1:15 P.M. showed slight right axis deviation. U waves were seen in Leads I, II, and CF_4. The T waves were diphasic in Lead III. A tracing taken four hours later showed the T waves to be upright in all leads. The T waves in Lead II were 4.0 mm. high, in contrast to 1.0 mm. in the first tracing. The T waves were now of normal configuration and the U waves were extremely low. A tracing taken on Nov. 14, 1945, at 8:00 A.M. was identical with the tracing taken at 5:15 P.M. the previous day. There was no change in the Q-T interval in these tracings. The tracings were taken during the terminal portion of the attack and consequently show but slight changes from normal. An electrocardiogram taken several weeks after the attack was over showed no change from the last tracing.

DISCUSSION

As pointed out in the review of the literature, findings in abnormal states associated with low serum potassium have been striking but not uniform. Prolongation of the P-R interval, intraventricular block, prolongation of the Q-T interval, depression of the RS-T segments, and a decrease in height and change in form of the T wave are present. There is evidence that the electrocardiogram in such states has some degree of specificity. Tracings in Case 1 taken in separate attacks six years apart showed a remarkable constancy, with tracings in the interval being normal. Tracings in Case 2, however, showed only a nonspecific change in the T waves.

We should like to add to the group of abnormalities already enumerated the appearance of a U wave during the hypopotassemic state. Case 2 shows this finding well. In the case reported by Stroll and Nisnewitz,[5] a tracing taken by them on June 23 at 9:33 A.M. showed a U wave in Lead II. Brown and associates[6] called attention to the appearance of a U wave in Lead CF_4 of one of their patients. Though the significance of this finding is not clear, its association with the other abnormalities of ventricular depolarization and repolarization is of interest.

The striking prolongation of the Q-T interval in Case 1 deserves special comment. This finding is particularly well shown because of the relative bradycardia. The tracings presented by Stewart and associates[4] were taken with the photographic paper moving at a more rapid speed and showed a lesser degree of prolongation. The unusual contour of the T wave is associated with the prolongation of the Q-T interval. Unipolar limb leads in familial periodic paralysis, not previously reported, are shown in Fig. 3 and emphasize this point. Q-T changes in Lead aV_L seem almost insignificant but are marked in Lead aV_F where the Q-T interval is considerably longer and is associated with increased height of the T wave.

Finally it might be worth while to consider whether or not there is any degree of specificity in the electrocardiogram in hypopotassemia. Common

to the small number of tracings so far reported are prolonged conduction times and changes associated with cardiac depolarization and repolarization. Prolongation of the P-R interval, intraventricular block, and RST-T abnormalities occur, but with no uniformity from patient to patient. Sequential changes dependent on the level of serum potassium are correlated in one of the cases which we are reporting. The findings which appear to us most characteristic of hypopotassemia are prolongation of the Q-T interval, depression of the RS-T segment, and low, rounded T waves.

CONCLUSIONS

1. Two cases of familial periodic paralysis are reported and the electrocardiographic findings correlated with low levels of serum potassium.

2. Prolongation of the P-R interval, intraventricular block, depression of the RS-T segments, lowering and change in form of the T waves, and prolongation of the Q-T interval may all be present in hypopotassemic states and represent profound changes in conduction, depolarization, and repolarization in cardiac muscle.

3. Prominent U waves associated with low serum potassium may be observed in familial periodic paralysis.

4. There appears to be a characteristic change in the electrocardiogram in familial periodic paralysis during an attack consisting of depression of the RS-T segments, a marked prolongation of the Q-T interval, and lowering and rounding of the T waves. This combination is a rare electrocardiographic finding. In contrast to the other hypopotassemic states, the electrocardiographic changes are spontaneous, transitory, and reversible.

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COMPLETE HEART BLOCK COMPLICATING PREGNANCY

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INSTANCES of varying degree of auriculoventricular heart block are not uncommon, but complete heart block as a complication of pregnancy is rare and justifies individual case reports. In 1938 Jensen[1] was able to collect only fourteen cases from the literature. One of the most interesting of these reported cases was presented by Herrmann and King.[2] Their patient had had complete A-V heart block since the age of 20 years and had had six successful, uncomplicated deliveries. Diddle[3] in 1941 added another case. Hamilton[4] encountered only two cases in an experience of twenty years. In 1943 Mitchell[5] found only one instance at Kings County Hospital in 17,862 deliveries. This occurred in a patient who apparently had a patent interventricular septal defect. In 1946 Quintin reported a patient with complete A-V block who had had two pregnancies which terminated in normal deliveries. Recently Eastman[7] reported his observations on a 36-year-old patient, eight weeks pregnant, with complete heart block, who had had eleven attacks of unconsciousness in the previous two years. No etiological factors could be established, but evidence indicated that the heart had been normal before the first Stokes-Adams attack two years prior to the admission. Therapeutic abortion was performed chiefly because of the numerous Stokes-Adams seizures and strong evidence of a very low cardiac functional reserve.

Complete heart block is comparatively rare, even in a general series of patients with cardiac signs and symptoms. White[8] found only seventy-nine such patients in 10,000 cases between the years of 1916 and 1930 at the Massachusetts General Hospital.

We wish to report an additional case in which a pregnancy terminated successfully in a normal delivery. The etiology in this case was not apparent, but a previous probable rheumatic fever seemed the most likely causative factor.

CASE REPORT

On Oct. 25, 1946, a 38-year-old patient came to the Obstetrical Clinic for an initial prenatal examination. Her last normal menstrual period had occurred on March 30, 1946. Her previous personal history was negative, with the exception of the following: an unexplained, undiagnosed,

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febrile condition with temperature ranging from 99°F. to 101.5°F. daily, which lasted four months, had occurred at the age of 18 years, while the patient was a student at college. There was no history of epistaxis, joint pains, or swelling during, or subsequent to, this febrile period. The patient taught school for thirteen years following graduation, during which time she felt well. In 1941 she had a sore throat with high fever. One previous normal pregnancy occurred in 1942. The post-partum course was uneventful. Following this pregnancy, the patient felt well until approximately two years before the onset of the present pregnancy. At that time she noticed symptoms of shortness of breath, palpitation, easy fatigability, and a feeling of tiredness upon ordinary exertion. This was not accompanied by anginal pain. These symptoms persisted and increased gradually in intensity until the pregnancy in which we studied her developed.

On Oct. 25, 1946, physical examination revealed an intelligent, slightly apprehensive, well-developed, well-nourished white woman. The thyroid gland was slightly enlarged and symmetrical. The heart was enlarged slightly to the left by percussion. No definite thrill was felt. Auscultation revealed a Grade 3, prolonged, harsh systolic murmur at the apex of the heart which was transmitted to the left axilla. The first sound at the apex varied in intensity and character. The second pulmonic sound was loud and greater than the second aortic sound. The radial pulse rate was 52 per minute. The blood pressure was 128/70. There was no peripheral edema.

Laboratory findings were normal. Chest x-ray and fluoroscopic examinations showed a prominent pulmonary conus and cardiac enlargement.

The electrocardiogram made on Oct. 30, 1946, showed a ventricular rate of 46 and an auricular rate of 75 per minute (Fig. 1). Complete A-V dissociation was present. A second electrocardiogram, Nov. 15, 1946, showed similar findings.

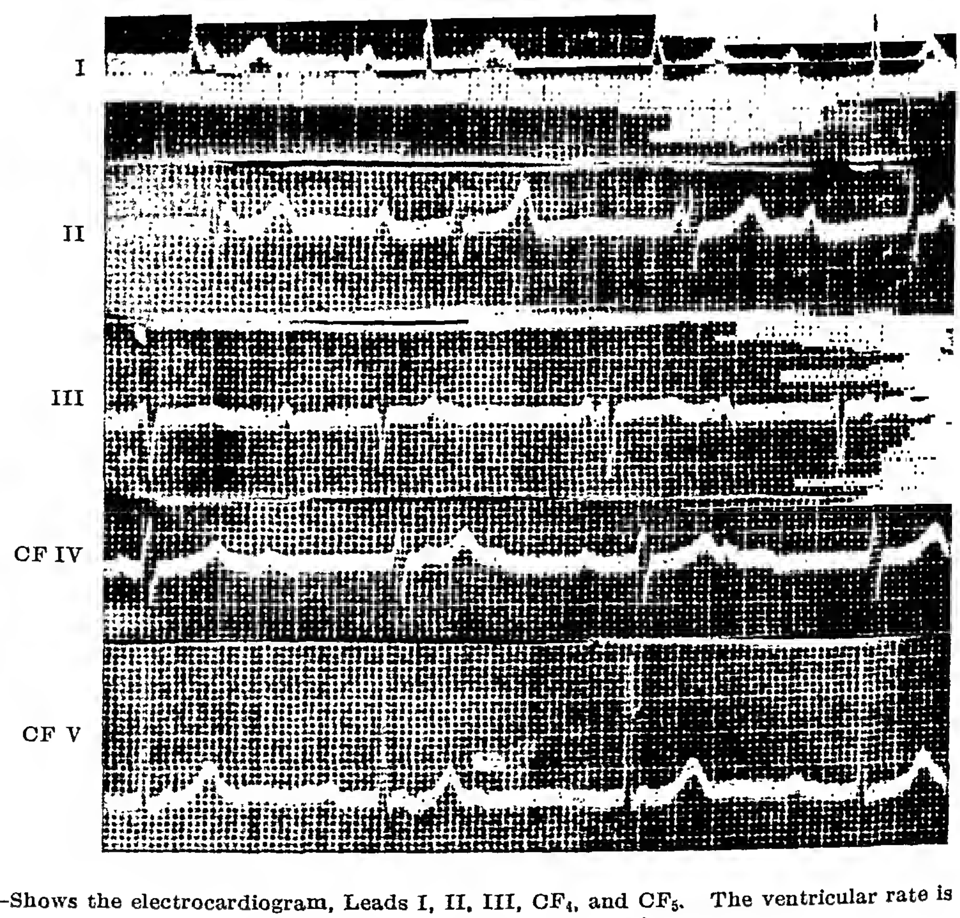

Fig. 1.—Shows the electrocardiogram, Leads I, II, III, CF_4, and CF_5. The ventricular rate is 46 and the auricular rate is 75 beats per minute.

The patient's ordinary physical activities were ordered to be moderately restricted and the more strenous habitual efforts were to be discontinued.

The patient was admitted to the hospital to enable closer observation and management three weeks prior to the anticipated date of delivery. The pulse rate was 54 beats per minute. The blood pressure was 140/80. Heart findings were unchanged on physical and electrocardiographic examinations. After five days in the hospital, the patient stated that she felt considerably better.

The onset of labor was spontaneous. Continuous caudal procaine anesthesia, using the nylon catheter technique, was instituted. Two hours later a living, full-term, normal, female infant, weighing 7 pounds and 8 ounces, was delivered from a plus three station, by low forceps, after a median episiotomy.

Blood pressure, respiratory rate, and pulse rate remained constant throughout the delivery. No dyspnea, orthopnea, shock, pulmonary edema, or dependent edema occurred in the immediate, early, or late postpartum period. After twenty-four hours the patient was permitted to walk. She experienced a completely normal and uneventful recovery.

The electrocardiogram on Jan. 8, 1947, showed a ventricular rate of 47 and an auricular rate of 72 beats per minute, with persistence of a complete A-V block. Her basal metabolic rate was +4 per cent. Physical examination of the heart revealed no change.

On Feb. 17, 1948, the patient was seen after one year and was feeling well but conscious of slight shortness of breath on exertion. The cardiac findings were unchanged, as was the electrocardiographic picture.

DISCUSSION

Experience with this case, in addition to that reported by others, suggests that complete heart bock, in the absence of symptoms or important complications, is not a contraindication to pregnancy, but the occurrence of Adams-Stokes attacks raises a serious question. Patients with heart block and pregnancy should, however, be evaluated frequently by the obstetrician and the cardiologist. Electrocardiographic studies should be made frequently. Cardiac decompensation should be treated immediately and termination of pregnancy considered. Evidence of a changing block would indicate a graver prognosis. The insurance of sufficient mental and physical rest, and avoidance of overexertion, fatigue, and cardiac decompensation as far as possible are considered mandatory for the proper conduct of such a case. The patient must be thoroughly instructed and impressed with the necessity of adequate prophylaxis and treatment of all respiratory infections. Prolonged exhaustive labor should not be permitted.

SUMMARY

1. The case history of a pregnant woman with complete A-V heart block has been presented.

2. The pregnancy and delivery were normal and uneventful.

ADDENDUM

Since this paper has been submitted for publication, two additional cases of complete heart block in pregnancy have been reported, making, with this presentation, a total of twenty-nine patients.

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PAROXYSMAL TACHYCARDIA WITH A VENTRICULAR RATE OF 365 PER MINUTE

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PAROXYSMAL tachycardia is a well-known clinical entity. Depending on the site of origin, several different types of paroxysmal tachycardia have been classified. The differential diagnosis can be suspected clinically, but is established with certainty only from the electrocardiogram. It is of practical importance to establish the correct diagnosis since paroxysmal tachycardias are usually amenable to treatment and proper therapy may be life saving at times. The most common type is auricular tachycardia. In this condition, the heart rate is usually between 160 and 180 and rarely above 200 per minute. In infants, however, an extraordinarily rapid rate may be encountered,[4] and instances of rates of over 300 per minute have been recorded. We have recently encountered an infant with a supraventricular type of tachycardia in whom a ventricular rate of 365 per minute was demonstrated. As far as we can learn, this is the fastest human ventricular rate ever recorded. The diagnosis was not established until late in the illness. The importance of suspecting this condition is emphasized by the tragic outcome of our case.

CASE REPORT

M. T., a 5-week-old girl, was admitted to the Staten Island Hospital on Sept. 30, 1947. She was born on Aug. 21, 1947, full-term, without complications. Her health was excellent until ten days before admission when her mother observed episodes of respiratory difficulty lasting for an average of thirty minutes. During one of these attacks a local physician was summoned and "a rapid heart rate" was noted. The exact rate, however, was not recorded and no definite diagnosis was expressed. Between attacks the child was examined by her family doctor and she seemed perfectly normal. Because the attacks seemed to be related to feeding, a change of formula was advised. On the date of admission she again experienced one of her attacks of respiratory distress and within a short time was admitted to the hospital.

On admission the most striking features were the rapid, labored respiration, cyanosis, and a distended abdomen. The temperature was 97.4° Fahrenheit. The chest and lungs were normal to auscultation and percussion. The heart sounds were observed by the admitting physician to be "rapid and regular." No murmurs were heard. Because of the rapid type of respiration, the examination of the heart was not considered satisfactory and the significance of the tachycardia was dismissed. The liver and spleen seemed to be slightly enlarged. The neurological examination disclosed no abnormalities. The lips and fingernail beds were definitely cyanotic.

The red cell count was 4.5 million and the hemoglobin measured 85 per cent (Sahli). The white blood cells were 19,700, of which 31 per cent were neutrophiles and 69 per cent lymphocytes. There were 21 normoblasts per 100 white cells and the red blood cells showed some anisocytosis and poikilocytosis. A roentgenogram of the chest (Fig. 1) demonstrated some increased lung markings, and a diagnosis of bronchopneumonia was reported by the roentgenologist. The child was given 5,000 units of penicillin intramuscularly every three hours and continuous oxygen was administered. Her color improved, but the respirations were still rapid and labored.

Fig. 1.—Roentgenogram of the chest taken on day of admission.

The next day her temperature rose to 101° Fahrenheit. The liver was now definitely enlarged and there were many moist râles throughout both lungs. Because of the lack of response to therapy and obvious signs of congestive heart failure, attention was now directed to a more careful examination of the heart. The attending pediatrician believed that the heart rate was well over 300 per minute and for the first time, a diagnosis of paroxysmal tachycardia was entertained. A cardiac consultant confirmed this impression, and immediate digitalization was ordered. Unfortunately, the child expired before therapy was commenced. An electrocardiogram (Fig. 2) was obtained just before death. The tracing showed a ventricular rate of 365 per minute. The rhythm was definitely supraventricular and there was a ventricular response to each auricular beat, that is, a 1:1 response. The rhythm was probably auricular flutter, but it was not possible to rule out paroxysmal auricular tachycardia.

An autopsy was obtained and no anatomic defects were found. The ventricular and auricular musculature, both grossly and microscopically, presented the usual normal structure. The lungs were injected but demonstrated no evidence of bronchopneumonia. There were no congenital anomalies.

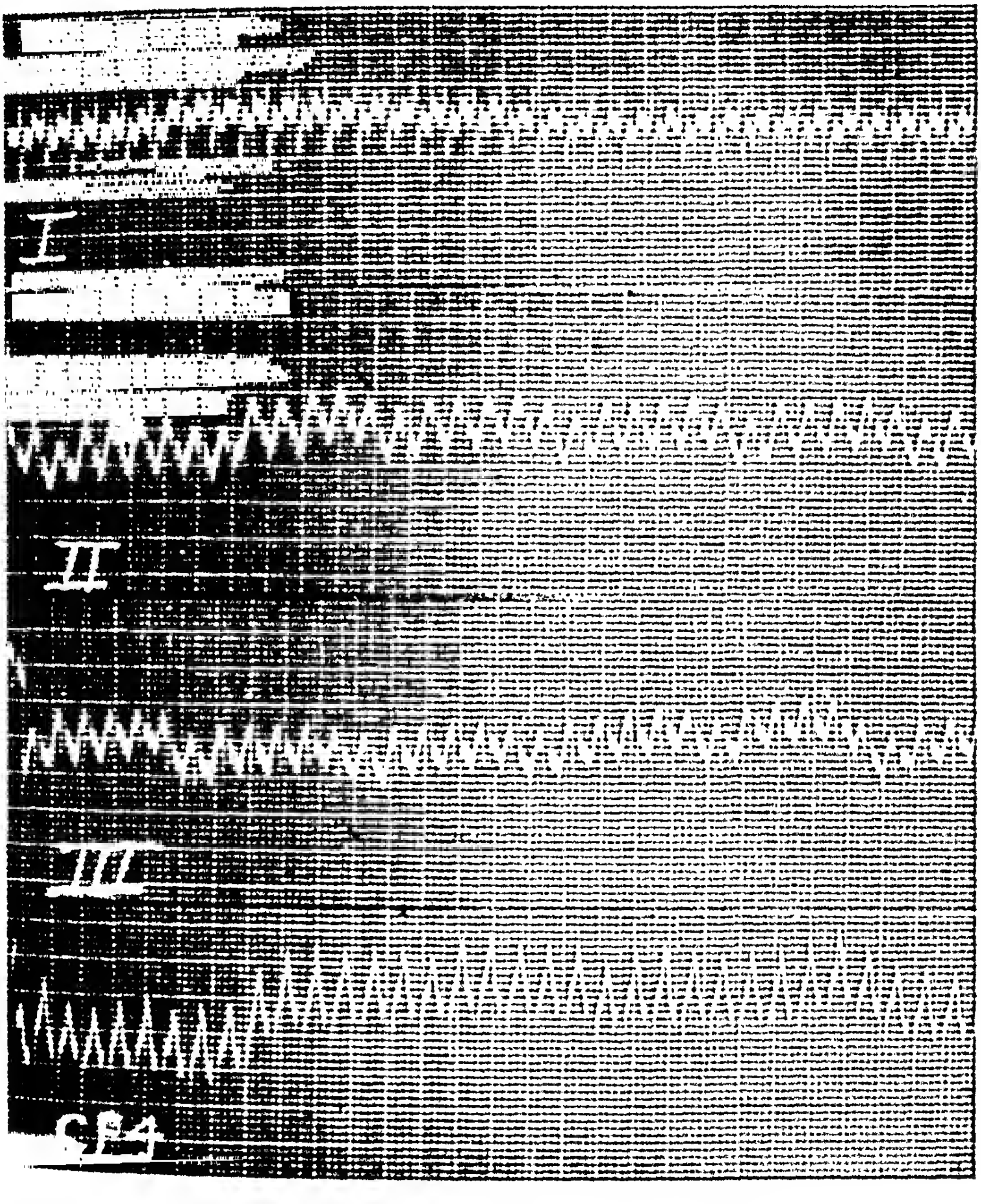

Fig. 2.—Supraventricular tachycardia. Rate, 365 per minute.

DISCUSSION

Extreme ventricular rates of over 300 per minute are rare. In 1943 Edeiken[1] in a review of the literature, collected seventeen cases in which the ventricular rate was over 300. It is interesting to note that twelve of these occurred in infancy.

In 1921 Lewis[3] showed that when the auricle of a mammalian heart was stimulated at about 250 *to 300 per minute*, a state of partial refractoriness developed; that is, not all groups of muscle fibers contracted. With a more rapid rate of stimuli, the refractory period was further increased, and when the rate reached a critical level of 450, a 2:1 rhythm occurred in the auricles. In a similar way, the A-V node also demonstrated a refractory state. Lewis, however, found the critical rate for the A-V node to be 270 to 300 per minute. Impulses stimulating the auricle at rates above 300 per minute failed to be transmitted by the A-V node, thus resulting in a slower ventricular response. From these observations, therefore, in all supraventricular tachycardias one should expect a ventricular rate not to exceed 300 per minute. This critical rate, however, does not seem to apply to infants. No explanation is offered for this difference in infancy, but it is possibly related to the size of the muscle fiber and the glycogen content of the node. According to Lewis[3] the length of systole, duration of the refractory period, and rhythmicity increase as the fiber and glycogen content decrease. A nodal fiber is smaller and has less glycogen content than is found elsewhere in the heart. In the majority of instances of extreme tachycardia in infants, organic heart disease has not been demonstrated. Before final conclusions can be drawn, special studies, including biochemical analyses, should be performed on all cases coming to necropsy.

The diagnosis of a paroxysmal tachycardia in an infant can easily escape detection. In the very young the heart rate is highly labile. Normally, the heart rate of a newborn infant is over 130 per minute. This rate rises sharply with excitement and infection, and unless one is careful, it is easy to attribute a rapid heart rate in an infant to some extracardiac cause. Furthermore, rates around 200 per minute are not easy to count, particularly in children who are difficult to manage and who have associated respiratory difficulties. It is well to remember that a shifting auricular flutter with a 2:1 or 3:1 response can give a deceptive ventricular rate. In spite of the accessibility of electrocardiographic apparatus, it is surprising how infrequently electrocardiograms are ordered on infants. In any tachycardia of unexplained origin, an electrocardiographic study is essential.

It is not the purpose of this paper to review the subject of paroxysmal tachycardia, *but mention should be made of a report by* Hubbard,[2] who described nine cases of paroxysmal tachycardia in infants under 1 year of age; six of the cases were encountered in a period of one year. It is of great importance to suspect paroxysmal tachycardia in any infant with a rapid heart action. It should also be realized that the attacks may be brief, and between attacks the child may be perfectly normal. However, if these attacks are unrecognized and continue, congestive heart failure may supervene. Congestion of the lungs, as in our case, may be mistaken for bronchopneumonia. Early enlargement of the liver in infants is difficult to interpret. Because of the anoxia, central nervous system signs may predominate. The problem becomes further complicated if the child has an elevated temperature and a leucocytosis, findings which were both present in our patient.

The treatment of choice in paroxysmal tachycardia of infants is digitalis. The simple procedures, such as pressure on the carotid sinus or eyeballs or methods to induce vomiting, are rarely effective. Hubbard[2] recommends an initial dose of 0.05 to 0.1 Gm. of Digifolin intramuscularly. Repeated doses may be necessary.

Paroxysmal tachycardia in infants may be more frequent than the literature indicates. It is possible that in certain instances, sudden unexplained death in infants may be on the basis of unrecognized paroxysmal tachycardia.

SUMMARY

1. A fatal case of supraventricular tachycardia in an infant with a ventricular rate of 365 per minute is presented. As far as can be learned, this is the fastest human ventricular rate ever recorded.

2. The condition was unrecognized until just before death. The signs of congestive failure, which were respiratory difficulty, cyanosis, and congestion of the lungs, were misinterpreted. No evidence of organic heart disease was found at necropsy.

3. Paroxysmal tachycardia is not rare in infants. The condition is amenable to treatment. A suspicion of this condition should be entertained in any child with an episodic history of cyanosis and respiratory difficulty. The more frequent use of the electrocardiogram in infants is recommended.

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CONTRIBUTION TO THE PATHOGENESIS OF CHRONIC COR PULMONALE

Report of a Case With Multiple Aneurysms, Intravascular Bands, and Old Massive Thrombosis of the Pulmonary Artery

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COR pulmonale or pulmonary heart disease refers to the effect upon the heart of changes in the lungs. These changes include alteration in the bony thoracic cage, diseases of the parenchyma of the lung, and diseases of the pulmonary vascular system. Diseases of the lung influence the heart function by obstructing the flow of blood through the lesser circulation. Normally the pressure in the pulmonary artery averages only about 20 mm. of mercury. Hence, to overcome resistance and maintain the pulmonary circulation, the right ventricle is not required to be as strong as the left. Once the pressure in the pulmonary circuit rises after obstruction it is reflected in sclerotic changes in the vessel wall, and, if continued over a period of time, results in hypertrophy of the right ventricle. Of course, a sudden rise in pulmonary arterial pressure, such as occurs with multiple pulmonary emboli, may lead to acute dilatation and failure of the right ventricle. The pulmonary circulation may become obstructed at any point from the pulmonary valve on one side to the mitral valve on the other. Depending upon the cause, site, and duration of the obstruction to the pulmonary circulation, we may divide cor pulmonale into acute, subacute, and chronic types.

Acute cor pulmonale is manifested by dilatation of the right ventricle secondary to sudden massive obstruction to the pulmonary circulation. This is caused as a rule by extensive pulmonary embolism, which usually has its genesis in venous thromboses in the leg, abdominal, or pelvic veins. Fortunately, the lung substance has a tremendous vascular reserve and, as has been shown experimentally, more than one-half of the vascular bed must be occluded before any appreciable strain on the right heart becomes evident. Since the clinical course of acute cor pulmonale is rather fulminating in most instances, there is little permanent heart damage since the patient either recovers completely or succumbs to his illness.

Subacute cor pulmonale was described by Greenspan[1] and has been proposed by others as a clinical entity deserving of recognition. This type is usually produced by metastatic endolymphatic carcinoma invading the pulmonary

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arterioles and resulting in thrombosis and obstruction to the blood flow. In cases reported by Brill and Robertson[2] the right ventricle failed following a short period of strain. The heart in these cases may show slight hypertrophy, but as Thompson and White[3] have pointed out, it requires about two months of continuous strain before the muscle begins to show signs of hypertrophy. Admittedly, this type of cor pulmonale is rare and is included only for the sake of completeness.

Chronic cor pulmonale is associated with a sustained increased resistance in the pulmonary circulation produced by diseases of the lungs and pulmonary vessels or by anatomical deformity in the bony structures of the chest. Chest deformity secondary to kyphoscoliosis or thoracoplasty is not a common cause of cor pulmonale in this country. Kyphoscoliosis could be considered a factor in only one of sixty cases of chronic cor pulmonale reported by Spain and Handler.[4] Diseases of the parenchyma of the lung which may be associated with chronic cor pulmonale include emphysema, tuberculosis, pneumoconiosis, interstitial fibrosis, bronchiectasis, bronchial asthma, and multiple cysts.

Many studies have been carried out relative to the role of primary obstructive emphysema in the causation of chronic cor pulmonale. Emphysema appears to be the basic change in many instances, but after years of investigation there is still much speculation as to the exact mechanism. No single explanation is acceptable or applicable in all cases. Pulmonary arteriosclerosis has been proved to be a secondary factor. The fibrosis often accompanying emphysema is not constantly present and it usually does no harm unless it is of the fine diffuse type, in which case an obstructive emphysema is produced by involvement of the small bronchioles. It is difficult to assume sufficient anatomical obliteration of the vascular bed in emphysema to cause obstruction since there is such a tremendous vascular reserve, as we have already pointed out. An important factor other than strictly anatomical changes is the increased alveolar pressure in emphysema which compresses the small vessels and increases the resistance to blood flow. Thus, the influence of several factors must be considered in an attempt to explain cor pulmonale on the basis of emphysema. Advanced pulmonary tuberculosis is associated with chronic cor pulmonale in from 4 to 40 per cent of the cases, according to various reports. The wide variance may be explained by different methods of weighing and measuring the right ventricle in comparison with the left. After study of all the etiological factors, Higgins[5] concludes that an emphysema associated with fibrosis is the most plausible explanation. The same situation pertains in bronchial asthma, bronchiectasis, and silicosis. Thus, the importance of emphysema, whether primary or secondary, in the initiation of changes leading to chronic cor pulmonale cannot be overemphasized in any discussion of this disease.

Diseases of the pulmonary vessels may play a dominant role in the pathogenesis of chronic cor pulmonale. In some instances the primary vascular disorder is not obvious to gross examination, while in others the obstructing lesion is very evident. Among the lesions seen are sclerosis, either primary or secondary; infections such as arteritis, syphilis, and tuberculosis; thrombosis and embolism;

neoplasms; aneurysms; and malformations. Sclerosis of the pulmonary vascular system has been studied in detail by Brenner,[6] who reported secondary sclerosis to be a common autopsy finding in older individuals and of little clinical significance in the production of pulmonary hypertension. Primary vascular sclerosis on the other hand, is associated with hypertrophy of the right ventricle. A septic arteritis accompanies any suppurative lung disease regardless of its etiology. Syphilis of the pulmonary artery, which is a rare lesion, has been written of extensively in the literature particularly in association with Ayerza's disease. It affects the large branches and main stem of the pulmonary artery for the most part and the pathological picture resembles that seen in the aorta. Since there is little or no obstruction, it is not likely that uncomplicated syphilis could play a large part in the production of pulmonary hypertension. Tuberculosis involves the pulmonary vessels near a focus of infection or in the wall of a cavity. Here the vessels may become so weakened and dilated as to form aneurysms. Primary neoplasms of the pulmonary artery are rare, indeed. Secondary neoplasms may alter the pulmonary circulation by embolism or invasion. I have already alluded to this subject under subacute cor pulmonale. Recent thrombi due to propagation of an embolus are frequent autopsy findings. On the other hand, thrombi in the stem or main branches of the pulmonary artery are an extremely uncommon finding, although this finding is fairly common in the smaller branches. The same holds for "true" aneurysms of the pulmonary artery. Band formations may represent either congenital malformations or be formed during the process of organization and recanalization of a thrombus. The subject of aneurysm, thrombosis, and band formation will be discussed later in more detail.

In the foregoing paragraphs I have endeavored to review briefly the main factors leading to hypertrophy, dilatation, and eventual failure of the right ventricle. With this in mind, an unusual case with autopsy findings will be presented. The condition was based upon a combination of rare lesions in the intrapulmonary vascular system.

CASE REPORT

E. H., a 55-year-old white man, was admitted to St. Francis Hospital July 25, 1947, in cardiac failure. Five years previously he had been seriously ill for one month with "chest trouble" and swelling of the left leg. Since then he had been subject to intermittent spells of chest pain which might occur daily for a week only to disappear for a month or so. The pain was described as a compression beneath the breast bone extending to the neck and shoulders. It was not related to effort and, in fact, was worse at night. He had also noted shortness of breath upon exertion which had grown progressively worse and which was now accompanied by cough and swelling of the ankles. He was placed upon digitalis by his physician but had not improved. The past history and family history were noncontributory.

Admission examination showed a chronically ill man with dyspnea and rapid respirations. The neck veins were prominent. The skin showed a 1 plus pitting edema of the ankles and the entire left lower extremity was larger than the right. The lungs were clear. The heart was enlarged to percussion and an apical systolic murmur was audible. The rate was 65 and the rhythm was irregular because of many extrasystoles. The blood pressure was 144/85. The liver was enlarged two fingerbreadths below the right costal border and was slightly tender to palpation. Laboratory studies showed the following: negative blood serology; 5.27 million

red blood cells with 103 per cent hemoglobin; 11,400 white blood cells; negative urine; negative blood serology; and a tendency to right axis deviation and trigeminal rhythm in the electrocardiogram.

The clinical impression was right heart failure of undetermined etiology. The patient complained only of dyspnea and occasional chest pain. His condition was not considered critical. He ate well but was very restless. About twenty-four hours after admission he was found walking in the hall in a confused mental state. The nurse noted considerable dyspnea and cyanosis. Shortly after being returned to bed Cheyne-Stokes respiration developed; the pulse became imperceptible, and he expired a few minutes later.

Post-mortem Examination.—There was bilateral ankle edema and the left lower extremity was swollen. The abdominal organs were not remarkable except for congestion of the liver and spleen. The pleural cavities were free of fluid. Both lungs were voluminous, crepitant, and upon cut section showed an increased fluid and blood content.

The heart was markedly enlarged, measuring 11.5 by 13 centimeters. The epicardium showed small hemorrhages over the right atrium. The left ventricle was contracted, its wall measuring up to 1.5 cm. in thickness. The myocardium was reddish brown in color. The right ventricle

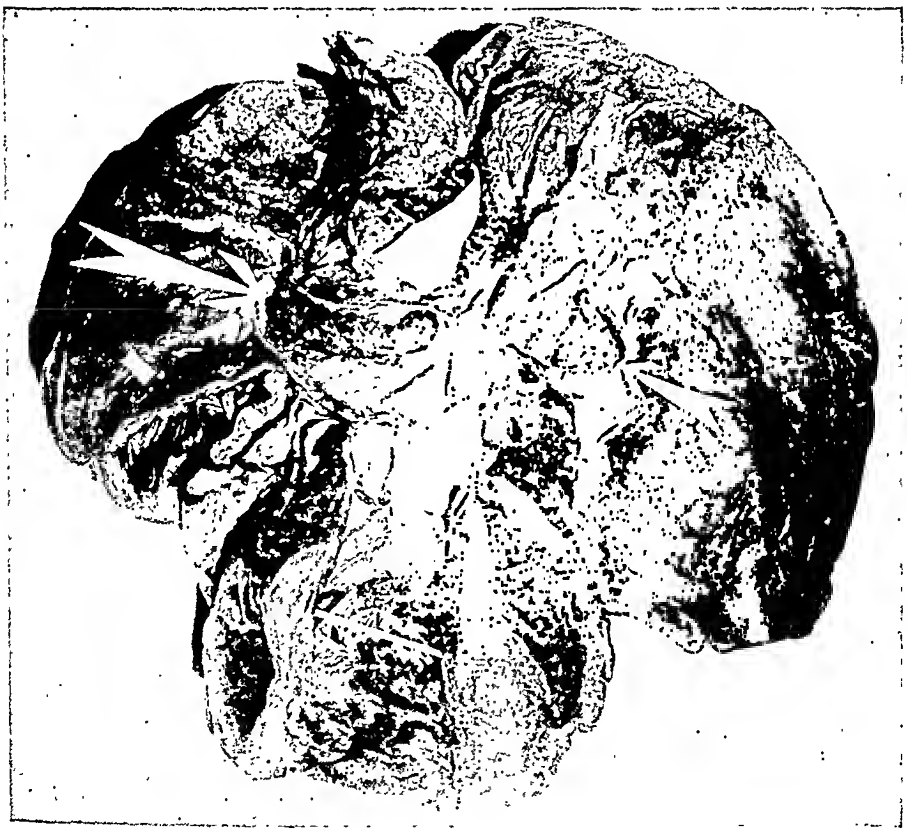

Fig. 1.—Heart and pulmonary artery opened. Note tremendous hypertrophy of right ventricle. Arrows point to large thrombi in both main branches and papers inserted beneath bring out the band formations at points of aneurysmal dilatation.

was enlarged, its wall measuring 1.2 cm. in thickness. The right atrium was also hypertrophic and contained several firm grayish-red thrombi. The valves were not abnormal. The coronary arteries and root of the aorta showed slight atherosclerosis. In both main branches of the pulmonary artery were huge, grayish-red thrombi firmly attached to the vessel wall. About both thrombi the artery showed aneurysmal dilatation, but the lumina were considerably narrowed.

The thrombus on the right measured 6.5 by 2.5 cm.; on the left, 5.5 by 4.0 centimeters. Distal to the thrombi all branches of the pulmonary artery showed many points of fusiform dilatation at which sites there were thin bands traversing the lumina usually at a right angle to the long axis of the vessels. These bands were filiform or flat and vessels as small as 3.0 mm. in diameter contained them. There was no evidence of smaller thrombi or pulmonary infarcts. The pulmonary artery showed considerable thickening and many atherosclerotic plaques (Fig. 1).

On microscopic examination, cross sections of the vessels showed considerable atherosclerosis of the large, medium, and small branches of the pulmonary artery. The arterioles in general showed intimal thickening, but the lumina were not constricted uniformly in many sections examined. The bands were found to be composed of hyalinized fibrous tissue for the most part with elastic and muscle fibers present but to a less extent. The muscle fibers were arranged with the long axis parallel to that of the band.

The necropsy diagnoses were: (1) Anomaly of pulmonary artery with multiple aneurysms and band formations. (2) Old massive thrombosis of both main branches of pulmonary artery. (3) Marked hypertrophy of right ventricle (chronic cor pulmonale).

COMMENT

This patient illustrates a type of heart failure produced by obstruction in the lesser circulation. Admittedly, obstruction due to this peculiar combination of aneurysms, thrombi, and band formations must be quite unusual. Indeed, the finding of any one of the three is in itself unusual. Therefore, it may be well to discuss each briefly with particular reference to pathogenesis.

Aneurysm of the pulmonary artery is a rare autopsy finding, as exemplified by a recent review of the literature by Deterling and Clagett,[7] who found it described only eight times in 109,571 autopsies. These same authors emphasize definite criteria for acceptance of an aneurysm as authentic, one of which is that, in addition to dilatation, the artery must show some evidence of organic degeneration. Most of the aneurysms reported are located in either the stem or main branches of the pulmonary artery. Changes which may lead to aneurysm of the pulmonary artery are not as important in the pathogenesis of cor pulmonale. For example, syphilis is an important cause of aneurysm while it plays a minor role in the pathogenesis of cor pulmonale. Cardiovascular anomalies are often associated with pulmonary aneurysm, particularly those in which a strain is thrown upon the pulmonary artery. Among those most frequently found are patent ductus arteriosus, septal defects, and aortic hypoplasia. In these cases the mechanism is clear in which a definite anatomical basis is found. It will be recalled that the aneurysmal dilatations in the case which is reported were seen only in areas where the bands existed. Since the bands were considered to be congenital anomalies, one assumes either that the aneurysms were also of congenital origin or that the aneurysms were the result of a developmental weakness of the vessel wall plus secondary factors such as increased pulmonary pressure with subsequent sclerosis. The importance of the aneurysms lies in a predisposition to thrombosis formation, as we shall see.

The incidence of thrombosis in the intrapulmonary arteries varies; it would seem to depend upon the thoroughness with which thromboses are sought at

autopsy examination. Thus, it is not uncommon to find thrombi in the small vessels; however, in larger vessels it is not common. Billings[8] found only eleven thrombi in 1,700 autopsies, making an incidence of around 0.7 per cent. We are not concerned with those instances of propagation following a recent embolus, but rather thrombi of such size as to obstruct the pulmonary circulation and of such duration as to result in chronic cor pulmonale. It is difficult to answer the question as to how much the pulmonary artery must be constricted to cause these changes. An entire main branch of the artery may be gradually occluded by thrombosis and yet be compatible with life if there is a concomitant hypertrophy of the bronchial arteries to compensate for the reduced blood supply to the lung. Means and Mallory[9] have reported a case exemplifying this. Other instances of marked narrowing of the pulmonary artery by old thrombi resulting in eventual right heart failure have been reported by Jump and Baumann,[10] Barnes and Yater,[11] and Covey.[12] There appears to be considerable controversy in the literature as to whether these thrombi arise in situ or from emboli. According to the consensus, most thrombi are embolic in origin while a few may arise in situ where there is local vascular damage. An aneurysmal sac provides an opportunity for thrombus formation. An arteritis, whether associated with local lung disease or caused by syphilis, may also be associated with thrombus formation. Atheromatosis does not predispose to thrombus formation in the pulmonary artery, where atheromatous ulcers are rare. In many instances of thrombi a source of embolization may be found if carefully searched for. In the present case it will be noted that this individual had a thrombophlebitis which began coincidentally with his chest trouble. Thus, there is a basis for both autochthonous and embolic types of thrombi. Study of the thrombus revealed evidence of lamination indicating an origin in situ. This problem, however, is more of academic interest than of practical value.

Just as the pathogenesis of thrombi is related to aneurysms, so band formations are related to thrombosis. Most bands are produced by an irregular rate of thrombus organization which allows small filaments of tissue to partially bridge the lumen of a vessel. Or, recanalization of a vessel after occlusion may convert the thrombus into many thin, bandlike structures. Möller[13] found iron-containing pigment in three of four cases reported, thus proving an origin from previous thrombi and not a congenital origin. Histologic study is important in disproving many cases reported as developmental anomalies. According to Saphir[14] only a few authors mention band formation in the pulmonary artery. When they occur just above the valve they are probably congenital in origin. In the few cases reported, detailed histologic study was not made to determine the true nature of the bands. It would be difficult to conceive of any other than a congenital origin for the bands in this case, particularly with regard to their histologic structure which lacked any changes seen in old organized thrombi.

SUMMARY

To recapitulate, cor pulmonale is the term applied to changes in the heart secondary to changes in the lungs. The basic mechanism is found in obstruction

to the normal circulation of blood through the pulmonary vascular system. This obstruction may result from diseases of the parenchyma or of the vascular system of the lungs. Depending upon the etiology, there are acute, subacute, and chronic forms of cor pulmonale. Chronic cor pulmonale usually develops when there exists chronic parenchymal disease with secondary vascular changes.

An unusual case, which showed congenital bands, aneurysms, and thrombi of the pulmonary artery, is reported in detail. The relationship of these findings to the pathogenesis of chronic cor pulmonale is discussed. Aside from its interest in showing extremely rare necropsy findings, this case illustrates the complexity of the problem we face in attempting to evaluate the role of various factors in the pathogenesis of chronic cor pulmonale.

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Abstracts and Reviews

Selected Abstracts

Moriyama, I. M., and Gover, M.: Statistical Studies of Heart Diseases. I. Heart Diseases and Allied Causes of Death in Relation to Age Changes in the Population. Pub. Health Rep. 63:537 (April 23), 1948.

The annual number of deaths from diseases of the heart (424,328 in 1945) is considerably more than twice the mortality from the second most frequent cause of death, cancer, from which 177,464 deaths resulted in 1945. About the year 1910 heart disease became for the first time the most frequent cause of death, and since that time, except for the period of 1918 influenza pandemic, it has been the unchallenged leader of the list.

In the forty-five years since 1900, the death rate for heart disease increased from 137 to 322 per 100,000 population, while the death rate for all causes dropped from 1,719 to 1,062 per 100,000 population.

It is significant that the major decreases in mortality since 1900 have occurred in the childhood and early adult ages of life. This tendency has been reinforced by the decline in the birth rate (up to about ten years ago) and the curtailment of immigration. During the period 1900 through 1940, the median age of the population of the United States increased from 22.9 to 29.0 years. The proportion of persons in the population 45 years of age and over rose from 19 per cent in 1900 to 27 per cent in 1940. Practically one-half of the deaths occurring at the present time are among persons in the definitely older age brackets.

The age changes affect the crude rates for specific causes of death to varying extents. Hence, when age-adjusted rates are computed for each cause, the increasing importance of heart disease in relation to other leading causes can be more meaningfully assessed. Diseases of the heart have progressed in the 40-year interval from third to first place, nephritis from seventh to fourth, cancer from eighth to second, and diabetes from eighteenth to eighth place, while tuberculosis, pneumonia, diarrhea and enteritis, diphtheria, and other communicable diseases have declined from higher to lower ranks.

Although there is some variation in the predicted crude death rate because of differences in the assumptions made, there is no question that heart disease will continue to play the principal role in the upward trend of mortality unless some revolutionary advance is made in medical knowledge bearing upon the prevention or treatment of cardiac diseases. If the age-specific mortality rates for heart disease in 1945 are applied to the estimated populations at specific ages in 1980, it is found that heart disease will cause 74 per cent more deaths in 1980 than it did in 1945. On a rate basis this increase would amount to 40 per cent, or a rate of about 452 per 100,000 population in 1980, in contrast to the 1945 rate of 321. It may also be estimated on the basis of a crude general death rate of about 14 per 1,000 population in 1980 that deaths from heart disease will constitute roughly 32 per cent of all deaths occurring in that year. BELLET.

Raymond, G. H., Adams, G. T., and McCorriston, J. R.: Venography in the Normal and Pathological Leg. Canad. M. A. J. 58:441 (May), 1948.

This study covers 113 venograms in 100 patients. Its purpose was to develop a technique by which structures can be identified and findings interpreted in normal subjects and by which pathologic changes can be demonstrated and identified.

The general appearance of the normal deep circulation is fairly accurately duplicated from case to case. Any notable deviation from the normal is considered pathologic and is evidenced broadly by a lack of filling of a part or all of the deep circulation and by a positive filling of the superficial system and the collaterals. It is now recognized that phlebothrombosis, in 90 per cent of cases, starts in the veins of the calf muscles and spreads via the deep circulation. A common observation in thromboembolic disease is the occurrence of vasospasm.

Venography may be used in acute cases of deep venous thrombosis; by it the apex of the obstruction can be outlined. In cases of chronic swelling of the leg of venous origin, the area of involvement and the collateral vessels can be demonstrated. The patency of the deep venous circulation may be demonstrated, so that treatment of varicose veins may be undertaken without fear of occluding the only venous return from the leg. Venograms can outline conditions before and after therapy. Two venograms can be done safely on the same patient on the same day.

There are, however, limitations to venography. The profunda femoris vein is not normally outlined; consequently, one is always uncertain as to whether or not it is the site of thrombosis. Then, too, there is some inconstancy of the connections of the long saphenous vein with the deep veins of the lower leg. On occasion, either the posterior or anterior tibial veins fail to fill, and this might lead the uninitiated to believe that a thrombus is then occupying the lumen. Certain dangers must also be feared: drug sensitivity, the possibility of dislodging a piece of the thrombus in an acute case, the possibility of infection, and the possibility of inducing thrombus formation.

Using 35 per cent Diodrast as the radiopaque contrast medium, after first testing the patient for sensitivity, the authors favor three techniques: (1) "Low" injection. (2) Bauer's method, when, for some reason, direct venipuncture is impractical. This consists of making a 1.0 cm. incision posterior to the lateral malleolus under local anesthesia and introducing the needle into the short saphenous vein under direct vision. (3) "High" injection, for the demonstration of upper femoral and iliac regions.

BELLET.

Makotoff, R., and Ross, G.: The Effect of Spinal Anesthesia on the Renal Ischemia in Congestive Heart Failure. J. Clin. Investigation 27:335 (May), 1948.

One of the effects of a decreased cardiac output in chronic congestive heart failure is a disproportionate decrease in the renal flow. The authors have calculated that the renal fraction of the cardiac output is reduced to about two-fifths of normal and have shown that there is a marked efferent arteriolar constriction. Merrill and co-workers have demonstrated that renin is present in increased amounts in renal venous blood of some patients with congestive failure. In the present study the authors endeavored to determine whether renal vasoconstriction might also result from neurogenic stimulation when the cardiac output falls. They blocked the autonomic pathways by means of high spinal anesthesia. The results indicated that the renal ischemia with marked efferent arteriolar constriction and the concomitant reduction in the renal fraction of the cardiac output which was regularly observed in established congestive failure were not maintained by sympathetic activity. That reflex vasoconstriction with shunting of blood from the kidney may operate in acute heart failure was not denied by these studies. Some workers have shown that neurogenic stimuli do affect the renal vascular bed. The authors suggest that the arteriolar constriction is mediated through some humoral mechanism (renin, according to Merrill and vaso-excitor material VEM, according to Shorr and associates).

LECKS.

Master, A. M., Weintraub, H. J., and Gertler, M. M.: The "Two-Step" and the "Anoxemia" Tests. J. Mt. Sinai Hosp. 15:21 (May-June), 1948.

The authors present a case which illustrates the result of the "two-step" and "anoxemia" tests in a patient with angina pectoris of seven years' duration, whose resting electrocardiograms had been normal during that period. The cardiac manifestations of coronary insufficiency produced by the two tests fall into three patterns: (1) temporary ischemia of the cardiac musculature, manifested by RS-T deviations and T-wave changes; (2) various arrhythmias, from isolated ectopic beats to paroxysmal tachycardias; (3) combination of (1) and (2). Almost all of the

cardinal electrocardiographic deviations indicative of coronary insufficiency were presented in response to the tests. On the basis of the criteria employed for each procedure, the response to the tests was positive for coronary insufficiency. The quantitative electrocardiographic changes produced by the tests were almost exactly the same. Ventricular tachycardia was encountered during both procedures. BELLET.

Adelman, M. H.: Cerebral Air Embolism Complicating Stellate Ganglion Block. J. Mt. Sinai Hosp. 15:28 (May-June), 1948.

The author presents the case of a woman, 43 years of age, who was admitted to the hospital for a diagnostic block of the right stellate ganglion. She complained of intractable pain of six years' duration localized in the right temporal, maxillary, and mandibular regions. It was decided that a diagnostic block of the right stellate ganglion was warranted, and the procedure was performed. A few seconds after the needle was removed the patient developed a syncopal attack. At the same time, she began to cough and to expectorate bright red blood. Oxygen was administered and the patient was kept in the Trendelenberg position. Because of the marked bradycardia, a vagovagal reflex was considered as a factor contributing to the clinical picture, and 15 mg. of ephedrine sulfate were administered intravenously. The pulse increased promptly to within normal limits. About ten minutes after the onset of this episode, the patient began to manifest the return of various reflexes. Speech returned about twenty minutes after the onset and the patient complained of inability to move the right upper and lower extremities. The patient was kept at complete rest for another hour, and during this interval the paresis in the right extremities disappeared completely. Three days later the patient returned for another attempt at stellate ganglion block. This time the posterior approach was used and a successful block was performed.

This case is another episode of cerebral air embolism following thoracic puncture, and offers a major argument against the use of the anterior approach to the stellate ganglion. Pneumothorax with penetration of the lung parenchyma is not an uncommon complication of using the anterior approach because the stellate ganglion lies behind the dome of the pleura which shows considerable variation in height. The posterior approach to the stellate ganglion offers less risk of penetration of pleura and lung parenchyma. BELLET.

Lowe, T. E., and Bate, E. W.: Hyperplasia of Cardiac Muscle Fibres. M. J. Australia 1:618 (May 15), 1948.

The occurrence of hyperplasia in mature cardiac muscle fibers has been a much disputed subject for many years. Most modern writers maintain that enlargement of cardiac muscle occurs only by fiber hypertrophy.

The authors report their observations on the heart of a 22-year-old man who dropped dead while dancing. In this heart they consider hyperplasia of the muscle fibers to have occurred. The heart weighed 2,340 grams. The most notable feature was the enormous left ventricular wall. There was a gross aortic valvulitis with marked stenosis. Histologic examination revealed evidence of syphilis of the aorta and chronic rheumatic myocarditis in all layers of the ventricular muscle. In the three inner layers of the left ventricle many of the cardiac fibers were split longitudinally into two smaller fibers, each with its own nucleus. There were also many fibers containing two adjacent nuclei. Measurements of the diameters of the cardiac muscle fibers in the left ventricular wall revealed a lack of uniform enlargement of the mean fiber diameter in the various layers. The fiber size in the outer layer was relatively normal; that of the three inner layers ranged toward a smaller fiber size.

The authors emphasize that the measurements given and the histologic appearances of the muscle led to two conclusions: first, that hyperplasia of cardiac muscle had occurred in some layers, and second, that the individual muscles of the ventricles had reacted independently to the disease state. KLINE.

Sellors, T. H.: Surgery of Pulmonary Stenosis. Lancet 254:988 (June 26), 1948.

This author records the clinical findings in a patient in whom the pulmonary valve was successfully divided. A youth of 20 years was suffering from advanced bilateral pulmonary tuberculosis; he also presented a typical clinical picture of the tetralogy of Fallot. An operative attempt along the lines suggested by Blalock for pulmonary stenosis was considered. In the lower part of the conus it was found that a firm structure was thrust from the ventricle into the pulmonary trunk with each heart beat, and this was interpreted as being an imperforate pulmonary valve. The infundibular region of the right ventricle was chosen as the area from which the valve could be best approached and several holding sutures were inserted, care being taken to avoid any branches of the coronary artery. A long tenotomy knife was then thrust between the stitches till it engaged the resistant valve or septum, which was incised and cut in two directions. Some sense of direction was gained by placing a finger over the conus area and gauging the distance of the knife from the surface, but it is possible that division on the deeper aspects was not as thorough as on the superficial aspects. The opening in the ventricle was closed with three linen thread sutures, using the preliminary stay sutures to control the hemorrhage. At the end of the operation the pulsation in the conus was more forceful and the well-marked thrill previously present was converted into one of much lower frequency and intensity, which was located in a different situation.

In spite of the lung condition, the patient's recovery was straightforward and he was definitely, though not completely, relieved from his cyanosis. There is no doubt that the operation could be improved on future occasions. A more appropriate tenotomy knife or valvulotome might be employed and bleeding might be controlled more accurately.

BELLET.

Durie, E. B., and Brodziak, I. A.: Necrotizing Vascular Lesions Believed to be Due to Hypersensitivity to Sulphadiazine. M. J. Australia 1:710 (June 5), 1948.

The authors present the clinical course and autopsy findings in a patient who was given 17 Gm. of sulfadiazine over a period of five days for the treatment of a fever of unknown origin. Histologic examination of the kidney revealed an increase in the cortex, which was almost completely filled with closely packed or confluent foci of inflammatory cells which had a central area of necrosis or surrounded a necrotic vessel. Very few glomeruli and occasional distorted tubules were present in the cortex. The essential lesion was a subacute necrotizing arteritis. Similar findings were noted in the spleen. The heart showed interstitial myocarditis, with edema and cellular infiltration of the perivascular tissue.

On the basis of comparable findings reported in the literature, the authors arrived at the conclusion that the findings were attributable to sulfonamide sensitivity. The case report emphasized the importance of increased caution in the prophylactic and therapeutic use of sulfonamide drugs, particularly for minor infections, and the early recognition of signs of hypersensitivity to such medication.

ABRAMSON.

Davis, D., and Ritvo, M.: Osteoarthritis of the Cervicodorsal Spine (Radiculitis) Simulating Coronary Artery Disease. New England J. Med. 238:857 (June 17), 1948.

The authors discuss the clinical and roentgenologic features observed in forty-three patients with substernal or precordial pain resulting from cervicodorsal radiculitis. Of these patients, twenty-three had been thought to have coronary artery disease before the correct diagnosis was established. The diagnosis was based upon at least two of the following criteria: symptoms with definite radicular characteristics, reproduction of attacks by pressure over the spine, or prompt response to orthopedic therapy. Approximately 75 per cent of the group were men; the average age was 52 years.

In addition to precordial or substernal pain, the majority had pain reference to the shoulder girdle, neck, or jaws. Suboccipital headache and vertigo were also common.

In most of these patients, the pain occurred in attacks, usually at night while the patient was in bed or after prolonged sitting. The pain was aggravated or mild attacks initiated by coughing, sneezing, straining, or various changes in posture. Anterior chest pain could be reproduced by spinal pressure in nineteen patients. In twenty-eight patients, response to orthopedic therapy was sufficiently striking to be of diagnostic significance. Tenderness in the region of the costochondral junction was another common finding.

The roentgenologic findings are described. Postural and osteoarthritic abnormalities in the cervical and dorsal spine occurred in much higher incidence than would be expected in unselected individuals of comparable age.

KAY.

Hurwitz, A., and Arst, D. B.: Mycotic Aneurysm of the Brachial Artery After Cure of Bacterial Endocarditis. New England J. Med. 238:903 (June 24), 1948.

The authors present a case of a successful removal of a mycotic aneurysm that developed in the left brachial artery of a patient with endocarditis due to a Type VIII pneumococcus.

Two weeks prior to hospital admission a 20-year-old man developed chills, fever, nausea, and vomiting which failed to respond to sulfadiazine therapy. When admitted to the hospital he was found to have fever, a cardiac murmur, nuchal rigidity, moderate clubbing of the fingers, and cyanosis of the nails. Each of two blood cultures revealed the presence of a Type VIII pneumococcus which was sensitive to 0.02 units of penicillin per cubic centimeter. Five subsequent blood cultures taken during the period of treatment and five taken at daily intervals after cessation of penicillin therapy showed no growth. The apical systolic cardiac murmur became less harsh and at times assumed a high-pitched quality. The patient was allowed to go to his home, but he returned to the hospital complaining of a sharp pain in the left axilla. The only new physical findings at this time were confined to the left upper extremity. These findings led to a diagnosis of occlusion of the brachial artery and the patient was given an initial dose of 300 mg. of Dicumarol, 50 mg. of heparin intravenously every four hours, and 200 mg. of Papaverine every two hours.

Two weeks after the patient's second admission, a fusiform enlargement was noted for the first time slightly above the previous site of occlusion, and oscillometric readings over this area were increased. In the next three days, there were several transitory episodes of numbness unrelieved by a stellate ganglion block. Examination revealed an increase in the size of the pulsating mass. There was definite weakness of all the muscles supplied by the median nerve and patchy hypesthesia to light touch and paresthesia to pinprick over the median sensory area. The diagnosis of an aneurysm of the brachial artery with compression of the median nerve was made and the patient was prepared for operation.

The pathologic diagnosis was chronic mycotic aneurysm of the brachial artery with organizing thrombus. The patient was discharged on the fifteenth postoperative day. The surgical removal of the aneurysm, which was found to be sterile at the time of operation, was followed by progressive improvement in the median nerve function.

BELLET.

Goldman, M. L., and Schroeder, H. A.: Immediate Pressor Effect of Desoxycorticosterone Acetate in Arterial Hypertension. Am. J. Med. 5:33 (July), 1948.

The present report deals with the effect of injections of desoxycorticosterone acetate and other related hormones upon the blood pressure of both normotensive and hypertensive human subjects. The recipients of the various injections were eleven hypertensive patients, five normotensive subjects, and four patients with coarctation of the aorta and normal diastolic pressures. The substances given intravenously in 5.0 mg. doses were desoxycorticosterone acetate, progesterone, Δ^5 pregneninolone, testosterone, dehydroisoandrosterone acetate, and 17-hydroxy-11-dehydrocorticosterone. In addition, the response of the blood pressure to a single intramuscular injection of 10 mg. of desoxycorticosterone acetate in peanut oil was followed for several days by the auscultatory method.

A significant, slowly developing rise in diastolic blood pressure followed the intravenous injection of desoxycorticosterone acetate in hypertensive patients. This rise became apparent about ten minutes after the injection and lasted from one-half hour to forty-eight hours. Other steroids used as controls did not show significant pressor effects when injected into hypertensive patients. In no case did desoxycorticosterone acetate cause a significant elevation of the diastolic pressure of normotensive subjects.

When several of the hypertensive patients were given a single intramuscular dose of 10 mg. of desoxycorticosterone acetate there resulted a significant rise in both systolic and diastolic pressures which lasted as long as forty-eight hours. In addition, these patients complained of exacerbation or intensification of their clinical symptoms, such as headache, nervousness, and restlessness.

KLINE.

Moloney, W. C., Murphy, A. S., and Harrington, W. J.: Prolongation of the Coagulation of Whole Blood by Dicumarol in Man. Am. J. Med. 5:40 (July), 1948.

Recent clinical observations raise the question of whether or not Dicumarol influences the coagulation of blood in a manner which is not accurately reflected by the prothrombin clotting time or by the clotting time of whole blood in glass tubes. In this report the authors investigated this problem employing glassware coated with a silicone (Drifilm) following the method described by Jaques and co-workers. Studies were carried out in a group of eleven male and female patients, of whom seven had multiple sclerosis, one had Friedreich's ataxia, and three had generalized arteriosclerosis. In most cases Dicumarol was given orally in dosage of 300 mg. the first day, 200 mg. the second day, and thereafter usually 100 mg. a day. Prothrombin clotting times were carefully performed using Quick's method. Whole blood clotting time was determined by a modification of the method of Lee and White. An arbitrary limit of clotting time of over 15 minutes in glass at 37° C. was considered abnormal; when Drifilm tubes were used, a clotting time of over 60 minutes at 37° C. was considered abnormally prolonged.

The authors found that following the administration of Dicumarol, an increase in the prothrombin clotting time usually occurred within forty-eight hours but the degree of hypoprothrombinemia varied considerably. Clotting time in Drifilm became definitely prolonged after forty-eight hours and when 700 mg. to 900 mg. of Dicumarol were given over a seven-day period, prolongation of the Drifilm clotting time for periods of from twenty-four to seventy-two hours or longer was observed. At the same time the clotting of whole blood in glass was prolonged slightly or not at all until very marked depletion of prothrombin occurred.

The authors emphasize that the clotting of blood as observed in glass represents an artificial and false reflection of the true state of intravascular blood coagulability. It was demonstrated that at prothrombin levels which were not low enough to influence the clotting time in glass, dicumarolized blood in drifilmed tubes took twenty-four hours or longer to clot. These observations provide laboratory support for the accumulating clinical evidence that Dicumarol may be effective in the prevention of intravascular clotting in dosages which are inadequate to produce critically low prothrombin levels or prolongation of the clotting time in glass. Unfortunately, the clotting test in Drifilm requires rather exact technique and for routine use is not a practical method at present.

KLINE.

Zeek, P. M., Smith, C. C., and Weeter, J. C.: Studies on Periarteritis Nodosa. III. The Differentiation Between the Vascular Lesions of Periarteritis Nodosa and of Hypersensitivity. Am. J. Path. 143:889 (July), 1948.

In their effort to differentiate periarteritis nodosa from necrotizing panarteritis, which is occasionally associated with hypersensitivity, the authors have distinguished two types of panarteritis, recognizable clinically and pathologically. One type is associated with hypersensitivity and is termed "hypersensitivity angiitis." For the other type the term "periarteritis nodosa" is retained. This report is devoted to the pathologic differentiation.

The authors wrapped silk around one kidney and removed the other kidney in sixty-two rats ("silk-perinephritis method"). When this technique was deviated from, for example, when one kidney was interfered with, typical lesions did not result. Usually the second kidney was interfered with on the same day or in one week or ten days, and only thereafter were typical lesions produced. Forty-three untreated rats constituted a control group.

The lesion in this group study was periarteritis nodosa, unassociated with hypersensitivity. It was observable in five stages, namely: (1) Fragmentation and focal edema of adventitial collagen at or near the bifurcation of muscular arteries; this occurred on the second or third day. (2) Adventitial infiltration by fibroblasts and histiocytes in the same areas, often spreading outward into adjacent fatty-areolar tissue. (3) Inflammatory exudation and necrosis, appearing first in the adventitia and outer half of the media. This was of "fibrinoid" appearance, followed by exudation of many eosinophils, but never of foreign body giant cells. Often thrombosis and sometimes aneurysmal weakening of the vessel wall followed the necrosis. These changes occurred in seven to eleven days. (4) Replacement of the necrosis by granulation tissue. (5) The scar or healed stage, possibly pathognomonic in the opinion of the authors, is featured by a proliferating fibrotic tissue filling the vessel lumen, often with canalization of the organized thrombus; a normal-appearing media; and adventitial scarring around the entire circumference or eccentrically placed. In many vessels at the hilum of a viscus, a mass of vascularized scar tissue replaced the entire arterial wall.

These lesions were found in their various stages mainly at the hilar sectors of visceral arteries; the pulmonary artery was never affected. Likewise, while the splenic artery and its main hilar branches were commonly involved, the splenic arterioles were free of the lesion. Finally, it is stated that, despite the rather definite schedule for the appearance of the five stages, all the various phases may be seen in a given case of long duration. This indicates the persistence of the exciting factor.

The authors compare this experimental lesion in the rat with the typical lesions of periarteritis nodosa in man and believe that they are identical, not only as to structural aspects, but also as to location and the time interval for the production of the various stages.

Their study on "hypersensitivity angiitis" is limited to human pathology, namely, in patients dying with asthma or after sulfonamide therapy. While admitting that in structural aspects the vascular lesions in such patients are very similar to those of periarteritis nodosa "in the third stage," the authors stress the difference in location, their common appearance in small vessels, arteriole and venule, in the lung, the spleen, and in the renal glomeruli, as well as in other viscera, and the relative freedom of the muscular arteries. They also emphasize the "one stage" appearance of the lesions of hypersensitivity in contrast to the varied appearance of "true periarteritis nodosa" in a case of long duration.

GOULEY.

Steiger, H. P., and Edeiken, J.: Further Observations of the Electrocardiographic Changes in Early Syphilis. Am. J. Syph., Gonor. & Ven. Dis. 32:391 (July), 1948.

In forty cases of early syphilis, electrocardiographic studies were made before, during, and in some cases after penicillin therapy. Seventeen (42.5 per cent) of the forty cases showed abnormalities either before or during treatment, and of these, eleven showed definite changes before penicillin treatment was instituted. The electrocardiographic abnormalities found consisted of T-wave and in some instances RS-T segment changes in the limb and/or chest leads; in no instance was there any evidence of interference in conduction. These changes occurred in all stages of early infectious syphilis. Eight patients showing no physical or serologic evidence of syphilis were treated with the same amounts of penicillin as the seventy syphilitic patients. None of these eight patients showed any electrocardiographic changes during penicillin treatment.

BELLET.

Kirgis, H. D., and Reed, A. F.: Temporary Interruption of the Sympathetic Impulses to the Head by Infiltration of the Cervical Sympathetic Trunk. Ann. Surg. 128:101 (July), 1948.

On the basis of anatomic dissections on thirty-three cadavers and clinical trial in 200 patients, the authors came to the conclusion that infiltration of a suitable anesthetic agent about the sympathetic trunk at the level of the tuberosities of the fifth or sixth transverse process was an effective means of blocking the sympathetic impulses of the head. The most generally successful procedure was the anterolateral approach, the needle being injected just posterior to the sternocleidomastoid muscle. The patient assumed the supine position with the head flexed and turned slightly to the opposite side. This made the bony landmarks easily accessible to the palpating finger. Frequently the tuberosities could more readily be felt by retracting the sternocleidomastoid muscle and the contents of the carotid sheath medially.

The actual technique consists of making a skin wheal along the posterior border of the sternocleidomastoid muscle, opposite the fifth or sixth cervical transverse process. The needle is then inserted and advanced until it is in contact with the lateral surface of the tip of the transverse process, then withdrawn slightly and reinserted along the anterior surface of the tuberosity. The injection is performed at a depth of approximately 0.5 cm. from the lateral extent of the transverse process. A typical Horner's syndrome usually appeared after injection of from 3.0 to 5.0 c.c. of a 1 per cent solution of procaine hydrochloride.

ABRAMSON.

Cesarman, T. E., and Martin, S. S. New Pharmacological Aspects of Salicylates. Arch. Inst. Nac. Cardiol. de México 18:373 (July 31), 1948.

Studies on normal subjects and rheumatic patients seem to prove that sodium salicylate and acetylsalicylic acid are eliminated slowly.

A new method of determination was used and its accuracy was demonstrated. The optimum blood level was attained with doses administered every twelve hours. A total dose of 0.1 Gm. of salicylate per kilogram of body weight was given in twenty-four hours and the concentration in the blood varied between 0.33 and 0.56 mg. per 100 cubic centimeters. Moderate doses of alkali made no appreciable change in the blood salicylate level.

LUISADA.

Terrier, J. C., Wakim, K. G., and Krusen, F. H.: The Effects of Occlusion With Various Pressures on the Blood Flow in the Lower Extremities. Arch. Phys. Med. 29:391 (July), 1948.

The present study was made in order to investigate the effects on the blood flow in the lower extremities, first, of single periods of five minutes of vascular occlusion at a pressure of 40, 80, or 120 mm. of mercury; and second, of periods of one hour of intermittent venous occlusion, applied at a rhythm of three minutes of pressure alternating with three minutes of release. The measurements of blood flow were taken by means of venous occlusion plethysmography.

Two series of observations were carried out on eight normal persons and on three patients whose circulation was moderately impaired by arteriosclerotic disturbances. After release of the occlusion with 40 mm. pressure, there were as many observations with a decrease of blood flow as there were with an increase. After release of the occlusion with 80 and with 120 mm. pressure, there were more observations with decrease than with increase of blood flow in either case. With intermittent venous occlusion the average final change of blood flow in all the observations was −5 per cent in the extremity treated with intermittent occlusion, and +9 per cent in the contralateral extremity, which was used as a control.

The authors conclude that under the conditions of their study a short period of occlusion for five minutes or intermittent occlusion for one hour with various pressures does not seem to have any significant effects on the circulation in the lower extremities.

KLINE.

Kayssi, A. I.: Death From Inhibition and Its Relation to Shock. Brit. M. J. 2:131 (July 17), 1948.

The author discusses the nature and mechanism of both primary and delayed shock syndromes, and of other phenomona related to quite different causes which are ordinarily confused with death due to inhibition. Formerly, it was common to speak of two kinds of death from inhibition, primary and secondary. The latter term was used to cover asphyxia and cardiac or respiratory syncope which was due to definite diseases to which the inhibition was regarded as being secondary.

The author reports that out of 2,000 sudden deaths, there were only two cases which he could not explain except by the mechanism of inhibition. This was supported by the absence of any pathologic, traumatic, or toxic signs, and also by the circumstances which surrounded the fatalities. Death from inhibition covers all sorts of sudden death occurring within a few seconds, or not longer than two minutes, after trauma or peripheral excitation which is relatively simple and not in itself sufficient to cause death. No pathologic changes which would be likely to account for death must be present at the subsequent necropsy. All medicolegal authorities are satisfied that this kind of death is explicable only on a basis of the "arrest" or "inhibition" theory by excitation of some part of the vagus. Certain regions are of particular importance and also there must be a special personal sort of constitutional susceptibility which varies from individual to individual.

The author emphasizes that death by inhibition is an entity.

BELLET.

Borrie, J., and Barling, E. V.: Treatment of Chronic Varicose Ulcers by Lumbar Sympathectomy. Brit. M. J. 2:203 (July 24), 1948.

The authors report the results of lumbar sympathectomy in four patients with long-standing chronic varicose ulcers. In all cases there were definite signs of associated vasospasm in the involved limb in the form of coldness and cyanosis of the skin. Preliminary lumbar paravertebral block uniformly produced marked cutaneous vasodilatation. Following operation, the ulcers became healed within three weeks and remained so throughout two winters. The authors also propose the view that when skin grafts are necessary, a preliminary sympathectomy will produce a much more favorable "soil" for the growth of the tissue. The importance of continuing to wear an elastic stocking after operation to protect the skin from trauma from without and edema from within is stressed.

ABRAMSON.

Nudelman, P. L., Left, I. L., and Howe, C. D.: Thrombopenic Purpura Following Quinidine. J.A.M.A. 137:1219 (July 31), 1948.

A 57-year-old white woman with hypertensive and rheumatic heart disease was treated with quinidine (0.6 Gm. daily) because of bouts of supraventricular tachycardia. There was no history of allergic disease, bleeding tendency, or previous quinidine therapy. After a total of 6.0 Gm. of the drug had been taken, gingival bleeding and generalized purpura developed, and the spleen became palpable. The bleeding time was prolonged to over 30 minutes; no clot retraction occurred in three hours; and the platelets numbered 4,000 per cubic millimeter. The erythrocyte count, total leucocyte count, hemoglobin concentration, and differential white cell distribution were within normal limits, and sternal marrow smear revealed no abnormalities. After quinidine was discontinued and a blood transfusion given, the platelets gradually increased in number, reaching 187,000 per cubic millimeter sixteen days after the development of the purpura. Following recovery, a test dose of 0.1 Gm. of quinidine was administered, and within three hours the platelet count dropped to 1,000 per cubic millimeter and purpura, epistaxis, and bleeding from the gums appeared. Six hours after the test dose, the platelet count fell to zero. Transfusion was again resorted to, and gradual recovery ensued.

The authors could find only one previous reference in the literature to thrombopenia following the administration of quinidine.

HANNO.

Orbach, E. J.: Clinical Evaluation of a New Technic in the Sclerotherapy of Varicose Veins. J. Internat. Coll. Surgeons 11:396 (July-Aug.), 1948.

The author describes a new technique for the injection therapy of varicose veins. This consists in the introduction of a small volume of air into the lumen of the vessel preceding the injection of the agent. This procedure prevents the initial dilution of the material by the blood. One cubic centimeter of air is aspirated into the syringe previously filled with the sclerosing agent while the syringe is held with the needle pointing upward. With the patient standing, the injection is made so that first the air and then the solution is injected. With regard to the possible danger of air embolism, the author points out that this never occurs when a small quantity of air is introduced into the saphenous veins or their tributaries.

A number of different sclerosing agents were studied, both the conventional and the air-block methods being used. The results indicated that with the air-block procedure a greater incidence of obliteration was obtained than with conventional methods. A new sclerosing agent, Sotradecol (sodium tetradecyl sulfate) was found to be quite effective when used with the new technique. An average dose of 0.4 c.c. yielded complete obliteration in 87.7 per cent of the injections. This compared favorably with the 83.8 per cent of successful obliterations obtained with an average dose of 1.7 c.c. of fatty acid solutions, such as sodium morrhuate and monoethanolamine. With the air-block procedure, no cases of slough followed, while with the conventional injection technique fifteen instances of postinjectional slough occurred. Such findings stressed the advantage of the new method in safeguarding against paravenous injections.

The importance of minimal thrombosis is pointed out, and methods are discussed in relation to the advantage of production of venous obliteration by intimal concretion rather than by organization of large thrombi. In this regard, it has been shown that a large thrombus is an ideal medium for recanalization. The distension of the veins after the injection of the sclerosing agent and the subsequent formation of large thrombi can be prevented by the application of firm bandages following treatment.

ABRAMSON.

Mannheimer, E., Carlgren, L. E., and Graf, W.: Further Experience With the Hypoxia Tolerance Test of the Heart in Children. J. Pediat. 2:58 (July), 1948.

The hypoxia tolerance test is performed by having the patient breathe 9 per cent oxygen for ten minutes and noting the effect of the test electrocardiographically and by means of the phonocardiogram. A positive result is based on some of the following changes: depression of the RS-T intervals in Leads I and II of at least 1.0 mm.; development of negative or diphasic T_1 or T_2; marked changes in the length of the P-R interval; and the appearance of gallop rhythm.

Studies were made in 365 children of whom ninety-one were considered to have normal cardiovascular systems and the remainder were children with rheumatic heart disease, active myocarditis of other etiology, and congenital heart disease (100 cases). With a few exceptions the test was negative in the normal cases. In active rheumatic carditis and active myocarditis of other etiology, about three-fourths of the cases gave positive results. Cases of healed carditis and of gallop rhythm gave a positive result in 25 per cent of the patients. Of fifty-three patients with patent ductus arteriosus, 64.1 per cent gave a positive result, whereas after operation, only 25 per cent reacted positively. Of twenty cases of cyanotic heart disease, only one gave a positive reaction to the hypoxia test.

JOHNSON.

Burgess, A. M.: Excessive Hypertension of Long Duration. New England J. Med. 239:75 (July 15), 1948.

The author notes the inadequacy of published data bearing upon the prognosis in essential hypertension, especially in the obviously nonprogressive type. The records of private patients with hypertension seen since 1914 were reviewed. Individuals were selected for study in whom systolic pressures of 180 mm. Hg or higher or diastolic pressures of 100 mm. Hg or higher had existed for at least eight years without established cardiac or renal disease or other evidence of progression. In 90 per cent of these patients, the hypertension had existed prior to 1932.

The average survival time was compared with average life expectancy of persons of the same age and sex. The group was then divided into three groups: living, dead, and incapacitated. They were also classified into groups according to age, sex, and degree of systolic and diastolic hypertension.

Of the original 100 patients, forty-seven are living and fifty-three are dead. The average expectancy of life was exceeded by twenty-eight patients, some of whom are still living. The average person of the group lived out almost a normal life span. Of persons over 65 years of age when hypertension was first noted, all outlived life expectancy. Of the thirty-two persons less than 50 years of age when the hypertension was discovered, the average duration of life was more than fifteen years, but appreciably less than the life expectancy for persons of this age, which is about twenty-six years. Because of the small size of the series, definite conclusions regarding the influence of sex were not drawn.

An elevated systolic pressure was not found to be especially unfavorable prognostically, even when pressures of 250 or over were observed. Conversely, in patients with a high diastolic pressure (120 or more on one or more occasions), the actual duration of life fell short of the normal expectancy by a considerably longer period than it did in the whole group.

Since forty-seven of the group are still living, the average duration of life for the whole group will lengthen; hence, the prognosis is actually more favorable than indicated by the data.

It is concluded that the individual with nonprogressive hypertension of at least eight years' duration lives to within three or four years of his normal life expectancy. Although individuals less than 50 years of age are less likely to live out a normal life span than older individuals, the average length of life for this age group is fifteen years after the discovery of hypertension.

This study has obvious significance in its bearing upon the selection of candidates for surgical management. A more extensive investigation, with the collaboration of a large number of physicians, is suggested.

KAY.

Major, S.: The Electrocardiogram in Catatonic Schizophrenia. New York State J. Med. 48:1489 (July), 1948.

This paper is concerned with the study of fifty-two schizophrenics, thirty-six of the catatonic, and sixteen of the hebephrenic type with catatonic episodes. The age was limited to 35 years to eliminate from the study any cases of latent coronary artery disease. In all cases, there was no evidence of cardiac disease.

The electrocardiographic findings departed from the normal in the following ways: extreme shortening of the P-R intervals; frequency of abnormal P and T waves in the chest leads; and the frequent occurrence of S-T segment depressions. Mixed electrocardiographic changes occurred many times in the cases described by the author. All of the patients in this study presented one or more signs of autonomic imbalance. It is probable that the electrocardiographic abnormalities under discussion are due to imbalanced autonomic activity causing alterations in the myocardial innervation and in the coronary blood supply.

BELLET.

Willius, F. A.: An Unusually Early Description of the So-called Tetralogy of Fallot. Proc. Staff Meet., Mayo Clin. 23:316 (July 7), 1948.

The author had previously credited the eminent Dutch physician, Eduard Sandifort, with the first description, in 1777, of the combination of congenital cardiovascular defects which is still known as the "tetralogy of Fallot." He now produces documentary evidence to show that the Dane, Niels Stensen, or Nicholas Steno, described this derangement in observations dated 1671-1672, his report antedating that of Sandifort by 105 years.

ARKLESS.

Edwards, J. E., Clagett, O. T., Drake, R. L., and Christensen, N. A.: The Collateral Circulation in Coarctation of the Aorta. Proc. Staff Meet., Mayo Clin. 23:333 (July 21), 1948.

The anatomy of the collateral system of arteries in coarctation of the aorta accompanied by a closed ductus arteriosus is discussed in this portion of the symposium. The authors show that the subclavian arteries, through the communications of their branches, play the paramount role in carrying blood from the part of the aorta above the coarctation to that part below the coarctation. The internal mammary, the intercostal, and the periscapular arteries bear the brunt of the anastomotic bridging. The anterior spinal artery has an important role. Contrary to usual statements, focal erosion of rib substance does not occur on the lower margin of the rib. It is observed on the inferior and anterior aspects of the main body of the rib, where it forms the wall of the costal groove.

Major disproportion between the size of the collateral channels on the two sides of the body may be used as a criterion in establishing the site of an unusual type of coarctation.

ARKLESS.

Christensen, N. A., and Hines, E. A., Jr.: Clinical Features in Coarctation of the Aorta: A Review of 96 Cases. Proc. Staff Meet., Mayo Clin. 23:339 (July 21), 1948.

Of 119 patients with a diagnosis of coarctation of the aorta, the records of ninety-six were considered to be adequate for this study. Male patients predominated in the ratio of 3.8 to 1 (76 to 20). The age range at the time of initial diagnosis was 4 to 59 years, although one individual who is being followed is now 67 years of age. Only 26 per cent were below the age of 20 years, the maximum deemed feasible for surgery.

High blood pressure in the upper extremities was the most frequent presenting symptom (43 per cent). Other complaints included dyspnea, headaches, vertigo and dizziness, tachycardia and palpitation, and nosebleeds. The abdominal aortic and peripheral arterial pulsations of the lower extremities were described as feeble or not palpable in 84 per cent. While the pusation of the large arteries is a more reliable guide to diagnosis in coarctation of the aorta than that of the smaller arteries of the legs, the converse is the more likely in occlusive arterial disease of the extremities. Pulsations of the arteries of the neck and upper extremities are frequently described as "bounding." Eighty-nine per cent of all patients had hypertension in the upper extremities. Six individuals of forty-nine had significant differences between the blood pressures in the two upper extremities. Positive evidence of collateral circulation was found in sixty-one of seventy-four individuals investigated. It was found most frequently over the scapular and interscapular regions.

Ninety-four per cent of all patients had heart murmurs. The most frequent was a systolic bruit heard best at the base of the heart but extending up to the neck and to the interscapular region of the back. When diastolic murmurs occur, associated defects should be considered.

Twenty-five per cent of individuals showed roentgenographic evidence of cardiac enlargement. About one-third of the cases gave electrocardiographic evidence of left ventricular strain. Normal ocular fundi were found in only 22 per cent of patients examined. Renal function was normal in the many cases studied, unless complications were present.

ARKLESS.

Borden, R., and Cooper, D.: The Roentgen Appearance of the Chest in Diseases Affecting the Peripheral Vascular System of the Lungs. Radiology 51:44 (July), 1948.

The small pulmonary blood vessels may be affected pathologically so that there is an increased permeability of their walls, which may or may not be associated with actual anatomic defects; or the pathologic changes may result in acute or progressive obstruction of their lumina leading to a marked reduction in the pulmonary vascular bed. The present paper deals with the first of these changes.

Trauma: Nonpenetrating chest injury has been followed by pulmonary complications. Roentgenographically, these patients show shadows ranging from localized dense lobar consolida-

tions to a patchy lobular density, usually with pleural involvement. These shadows are characteristically evanescent when due to edema or hemorrhage and their rapid disappearance in serial roentgenogram serves to differentiate them from changes due to infection.

Epidemic Influenza: Pathologically this is a classic example of an infectious agent acting directly upon the capillaries of the lung without producing anatomic change in the vessels. In serial x-ray studies done at six- to twelve-hour intervals an increasing haze is shown, enveloping the lungs from the periphery toward the hila, becoming more dense and confluent from hour to hour until no aerated lung remains visible.

Disseminated Lupus Erythematosus: Here the essential lesion is a fibrinoid degeneration of collagen throughout the body, associated with a necrotizing arteritis involving arterioles, particularly in the kidneys and heart, but also in many other organs, including the lungs. The character and progression of the shadows in the x-ray films of the chest may be indistinguishable from the picture of epidemic influenza.

Acute Rheumatic Fever: This is a collagenous degenerative disease with polyarteritis which selectively localizes in the heart but may also be found in many other organs. Although typical Ashoff bodies are not found in the lung, there may be multiple areas of perivascular exudation involving peripheral vessels which may heal and form perivascular nodules. The x-ray appearance is that of a diffuse haze involving the middle and upper portions of the lung fields in a rather symmetrical manner with the maximum density in the middle and outer pulmonic zone. If heart failure is present, the pneumonitic picture is obscured by the general vascular congestion.

Exfoliative Dermatitis: A condition caused by many toxic agents; it is nonspecific in its pathologic manifestations. Pulmonary symptoms are common during the acute phase of the illness. Chest x-ray findings may be that of a diffuse "inflammatory" process disappearing in a few days and reappearing during exacerbation of the diseased process. Since the toxic manifestations occur primarily in the small blood vessels of the skin and kidneys, it appears probable that similar focal vascular lesions account for the changes in the lungs.

Acute Glomerulonephritis: The vascular changes are not limited to one organ. If one postulates increased arterial pressure or increased permeability of the capillary walls, or both, as the cause of peripheral subcutaneous edema, a similar explanation may be offered for the transient pleural effusions and pulmonary changes which will frequently be found if chest films are obtained.

Periarteritis Nodosa: This is a disease syndrome with specific pathological findings and protean clinical manifestations. The histologic lesion is a focal arteritis. Most patients, if not all, will show pulmonary x-ray changes at some time during the illness. In the acute form, the pulmonary changes are associated with signs and symptoms of acute pulmonary failure. The x-ray shadows are massive and extend symmetrically from the hilum to the middle lung zone, giving the appearance of a "corona" around the mediastinum. It is thought that the sudden onset and the rapid clearing of these shadows are due to changes in permeability of the vessel walls such as occur in urticarial responses in the skin. In the chronic form, the x-ray changes are small, hazy shadows through the periphery of the lung fields associated with increased prominence of the pulmonary vascular markings. The peripheral and patchy nature helps differentiate it from inflammatory disease. Serial roentgen study shows a migratory pattern similar to Loeffler's syndrome.

Loeffler's Syndrome: This condition is associated with migratory pulmonary shadows on roentgenograms and an eosinophilia in the blood and sputum.

It is believed that conditions such as those discussed which have a similar background in pathology may also present a distinctive roentgen pattern in the lungs.

ZION.

Goodriek, W.: Pulmonary Edema. Radiology 51:58 (July), 1948.

Roentgenographically, pulmonary edema may simulate many other conditions. Although the roentgen changes may vary considerably, certain features help to differentiate edema from other pulmonary diseases. These consist of (1) the diffuseness of the shadows throughout the lungs, with the exceptions of the apices and bases; (2) variability of the findings in serial roentgen study; and (3) pulmonary vascular and cardiac enlargement.

Although pulmonary edema is caused by or associated with a wide variety of pathologic conditions, the present discussion is limited to cardiac failure, nephritis, and excessive parenteral administration of fluids. The basic physiologic changes in these conditions are, singly or in combination, (1) an increased intracapillary pressure, (2) decreased osmotic pressure, and (3) altered permeability of the capillary walls.

Pulmonary edema associated with left-sided cardiac failure is due to an increase in hydrostatic pressure and capillary permeability. The increased hydrostatic pressure is a result of the tamponade effect on the pulmonary veins produced by left heart failure, whereas the increased capillary permeability results from anoxia and neurogenic influences. The roentgen picture differs, depending on whether the failure is acute or chronic. In chronic failure, the increase in hydrostatic pressure is slower in appearance and the effect of gravity and stasis in the dependent parts of the lung causes edema to occur there first. Pleural effusion is a frequent accompaniment. The upper lung fields are usually clear, although the vascular markings are more prominent than usual. In acute cardiac failure, there is a pronounced increase of the lung shadows, as a result of the impaired venous return from the lung. The edema tends to occur in the central portions of the lungs. The apices and bases are usually clear and there is seldom any associated pleural effusion. The causes for central edema in acute left heart failure are not well understood. The possibility that this is the result of less excursion in this portion of the lung and, therefore, more stasis, is suggested.

Pulmonary edema associated with nephritis may be due to any one or a combination of the physiologic factors. With acute glomerulonephritis, edema may occur with normal serum protein levels, and with very little elevation of nonprotein nitrogen. Edema in these cases is due presumably to toxic factors. If pulmonary edema occurs, it is usually due to an associated cardiac insufficiency. With late terminal glomerulonephritis, there is an elevated urea nitrogen and frequently elevated blood pressure and cardiac failure. The physiologic defect responsible for pulmonary edema in pure nephritis without cardiac failure is an increased capillary permeability. Why some capillaries are affected and others are not, is not clear. The chest films in these cases show focal areas of edema which may be localized or diffuse. There may be little enlargement of the vascular shadows or those of the heart.

Large quantities of parenteral fluid may not be promptly excreted by the kidneys. The consequent increase in blood volume increases the hydrostatic pressure within the capillaries and causes diffusion of water, salt, and protein into the interstitial tissues. On x-ray examination, the heart is found to be enlarged. There is an increase in vascular markings in the lung fields. Pleural effusion frequently accompanies the pulmonary edema. The location and extent of the edema vary on serial examinations.

ZION.

Freis, E. D., Stanton, J. R., and Wilkins, R. W.: The Effects of Certain Dihydrogenated Alkaloids of Ergot in Hypertensive Patients. Am. J. M. Sc. **216**:163 (Aug.), 1948.

Three new dihydrogenated alkaloids of ergot (dihydroergocornine, dihydroergokryptine, and dihydroergocristine) have been found to lower the blood pressure of a significant percentage of hypertensive patients following intravenous injection. The most effective were dihydroergocornine and dihydroergokryptine. The degree and duration of hypotensive activity were extremely variable in different subjects.

These drugs have been shown to have sympatholytic, adrenolytic, and vagotonic properties: (a) Sympatholytic actions included the production of postural hypotension, the inhibition of hypertensive overshoots following depressor stimuli, diminution of reflex sympathetic vasoconstriction in the digits, and moderation of the cold pressor response. In addition, the drugs had a reduced hypotensive action following lumbodorsal splanchnicectomy. (b) Adrenolytic activity of dihydroergokryptine was demonstrated by inhibition of the hyperglycemic response to epinephrine, and, under proper experimental conditions, diminution of the pressor response, tachycardia, and mydriasis, following epinephrine. (c) Evidence of vagal stimulation or of unopposed vagal activity was manifested by bradycardia and, in some cases, by nausea and vomiting.

No serious toxic reactions were observed. Nasal stuffiness occurred in almost every case. With the dosage used, the other side effects, notably nausea, vomiting and faintness, occurred in approximately twenty-five per cent of the patients tested.

In selected cases dihydroergocornine was effective by the oral route, usually in doses approximately ten to twenty times greater than the effective intravenous dose. However, such effective oral doses are so large as to be, for the present, neither practical nor economically feasible. The most serious limitations to the clinical use of these drugs are the development of side reactions in some patients and the absence of significant hypotensive effects in others. In addition, the production of postural hypotension, which these drugs have in common with all other sympatholytic agents, imposes a hardship on the patient. Long-term studies are needed for further evaluation of clinical usefulness. The possibility of using this drug as a test agent in predicting the outcome of splanchnicectomy is under investigation at present by the authors.

DURANT.

Luisada, A. A., and Fleischner, F. G.: Temporal Relation Between Contraction of Right and Left Sides of the Normal Human Heart. Proc. Soc. Exper. Biol. & Med. 66:436 (April), 1947.

The temporal relation between the contractions of the left and right heart chambers was studied by means of fluorocardiography with the simultaneous recording of two pulse tracings on one strip. The study was performed on eight normal subjects and included the observation of the pulsations of the aorta, the pulmonary artery, both auricles, and both ventricles.

In all observations the contraction of the right auricle preceded that of the left auricle, and the contraction of the right ventricle preceded that of the left. The delay of action of the left chambers was found to be between 25 and 30 milliseconds.

AUTHORS.

Fischmann, E. J., and Gwynne, F. J.: The Heart in Rheumatoid Arthritis. Brit. Heart J. 10:125, 1948.

This study was stimulated by the conflict between the clinical rarity of cardiac lesions and their frequent presence at necropsy in patients with rheumatoid arthritis.

Sixty of 150 patients with rheumatoid arthritis were selected, after elimination of those without a typical picture, those with a history of rheumatic fever, those with chest deformity, and those unable to stand upright. All had advanced rheumatoid arthritis of considerable duration.

Only three patients presented clinical manifestations of heart disease. One had a mitral diastolic murmur but no symptoms of heart disease. The other two had heart failure presumably due to coronary artery disease. Mild symptoms, such as dyspnea and palpitation, in a few patients could be explained by the presence of anemia or general debility. One hundred thirty-one electrocardiograms were taken. One showed auricular fibrillation. Another had a P-Q interval of 0.22 second. Both of these were from patients sixty-nine years old. A third developed RS-T depression following chrysotherapy. Low voltage in the standard leads was the most frequent electrocardiographic abnormality. Five (8 per cent) had a voltage of 0.5 millivolt or less in all three leads. In eighteen (30 per cent) the voltage was 0.8 millivolt or less. Anemia and generalized wasting coincided with low voltage. Eight hearts were considerably enlarged and six moderately enlarged by roentgen study. Of these, seven had left ventricular enlargement alone, three had left ventricular and left auricular enlargement, and four had general enlargement of the heart. One had isolated enlargement of the left auricle.

The authors assume that the absence of clinical symptoms is related to a milder myocardial process due to (1) the age of onset, (2) reduction of physical performance due to joint involvement, and (3) more gradual development of the rheumatic process.

SOLOFF.

Duchosal, P. W., Ferrero, C., Doret, J. P., Andereggen, P., and Rilliet, B.: The Human Intracardiac Potentials Obtained by Catheterization. Cardiologia 13:113 (No. 3), 1948.

Three standard leads were taken simultaneously with the intracardiac potential by means of a four-channel electrocardiograph. The right arm was used as the site of the indifferent electrode for the intracavitary leads. Tracings were obtained in nineteen patients and one normal subject.

The potentials of the right atrium and ventricle are from 0.5 to 3.0 millivolts for the former, and from 8.0 to 30 millivolts for the latter. The size of the QRS complex diminishes considerably as soon as the electrode leaves the ventricle; the voltage of the P wave falls when the electrode is outside the auricle. The intra-auricular P wave never begins earlier than the P wave of the standard leads. The P wave obtained from the inside of the left auricle in a case of interauricular septal defect was positive and late. In auricular fibrillation, the intra-auricular leads sometimes show large, well-marked, regularly recurring auricular oscillations during periods of as long as two seconds; between these periods the oscillations are small and irregular. From this behavior one may conclude that interference of several components plays a role in this arrhythmia.

The ventricular tracing obtained from inside the right ventricle usually begins with a small R wave. In cases of right bundle branch block the intrinsicoid deflection is delayed from 0.04 to 0.10 second.

The majority of the premature contractions observed during the catheterization are ventricular. Their voltage is usually higher than that of the normotopic systoles and they originate in the right ventricle as evidenced by the immediate negativity of their QRS complex. Before the first signs of the presence of the extrasystole appear in the standard leads the intraventricular activity may already exist for 0.03 second and attain an amplitude of 10 millivolts. This fact is of considerable importance in confirming the theory of the distribution of electrical potentials of the heart to the periphery.

BRUMLIK.

DeCastro, G. L., and Carrascal, A. F.: Air Embolism and Its Treatment by the Intravenous Injection of a Carbon Suspension. Rev. Clin. Españ. 28:215 (Feb.), 1948.

The authors review the literature on air embolism and report two cases that developed severe cerebral manifestations with loss of consciousness and convulsive seizures following therapeutic pneumothorax. The first patient died while the second one recovered promptly after the intravenous injection of 2.0 to 3.0 c.c. of a fine suspension of carbon. This preparation serves to absorb the free gas and thus relieves the symptoms produced by the mechanical obstruction to blood flow in either the greater or lesser circulation. The carbon suspension should be injected slowly and a paraffinated syringe is required to prevent settling of the preparation.

The authors attempted to reproduce their single clinical cure experimentally in six rabbits without success. The animals died too quickly following the injection of air. "In vitro" experiments also failed to demonstrate the value of carbon suspension.

GOLD.

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EXECUTIVE COMMITTEE OF THE SCIENTIFIC COUNCIL

At its last meeting before the annual meeting in June, the Executive Committee of the Scientific Council recommended several changes in committee organization.

It was voted to discharge the present Committee on Films and Slides and replace it by a committee whose function would be the consideration of all scientific educational material either distributed or approved by the American Heart Association.

It was recommended to reactivate the Committee on the Standardization of Electrocardiographic Nomenclature to reconsider nomenclature and other pertinent matters of standards in this field.

Approval was voted for a committee to recommend standards for election of future members to the Scientific Council. Another action called for consideration of a method of rotating membership of the Advisory Board on Cardiovascular Diseases to the American Board of Internal Medicine and the appointment of new personnel to gradually replace those who have served more than three years, with due consideration given to representation of wider group disciplines.

Reporting on activities of the American Council of Rheumatic Fever, Dr. Rustin McIntosh cited two active projects in which the Council is now engaged. One of these is the maintenance on a continuing basis of the material collected on facilities and programs of care for rheumatic fever and rheumatic heart disease by the Helen Hay Whitney Foundation. The other project is a study of existing community rheumatic fever programs, primarily to evaluate the contribution these programs make to the medical care of persons with rheumatic fever and heart disease and to derive guiding principles of administration for satisfactory programs.

Dr. Norman E. Freeman, reporting for the Section on Circulation, stated that a Research Study Committee has been appointed with Dr. Eugene A. Stead, Jr., Chairman, Dr. Robert W. Wilkins, and Dr. Geza de Takats, to whom requests for grants-in-aid regarding the circulation will be referred.

TRAINING SCHOOL FOR CARDIOVASCULAR INVESTIGATORS

The Training School for Cardiovascular Investigators, in the Department of Physiology, School of Medicine, Western Reserve University, is now open to enrollment. Support of this program in cooperation with the National Heart Institute was announced in the April issue. Dr. Carl J. Wiggers, Director of the Department of Physiology, will be in personal charge.

A maximum of ten qualified graduates or undergraduates in medicine or related sciences will be accepted, the course to begin on July 1 or September 1, as enrollment warrants. There are no tuition fees and the Division of Research and Fellowships of the National Institute of Health in cooperation with the National Heart Institute will offer research fellowships to acceptable candidates who require financial support. The American Heart Association's allocation of $16,170 will cover the cost of the training program.

The year's planned training includes formalized technical training in research methods employed in cardiovascular studies on human subjects and animals (eight weeks), experimentation apprenticeship with the assistance of qualified investigators in basic animal research (eighteen weeks), supervised independent research (sixteen weeks), and supervised experience in preparation of manuscript (six weeks).

Inquiries or requests for applications should be addressed to Dr. Carl J. Wiggers, Western Reserve University School of Medicine, Cleveland 6, Ohio.

FIELD STAFF APPOINTMENTS IN PUBLIC HEALTH DIVISION

S. S. Lifson and W. George Gould have been appointed to the field staff of the American Heart Association's Public Health Division. They are now serving under Dr. John W. Ferree, Director of the Division, Mr. Lifson as Supervisor of Field Services, and Mr. Gould as Field Consultant.

Mr. Lifson, formerly associated with the National Health Council as Assistant Director of Community Organization, will assist in the development of field service programs and public health activities for affiliated heart associations. This is in line with the expanded program of community cardiac services now being developed among state and intermediate associations by the American Heart Association. Mr. Gould will assist in the organization of public health programs for affiliated heart associations in major areas throughout the United States. He is a former Associate Director, Division of Social Protection and Law Enforcement of the American Social Hygiene Association.

FOURTEEN NATIONS REPRESENTED IN NEW EUROPEAN CARDIOLOGICAL SOCIETY

Leading heart specialists from fourteen European countries met in Brussels late in January and formed the European Cardiological Society (Societe Européenne de Cardiologie).

The announced aims of the Society, which is open to qualified cardiologists throughout the continent, are "to foster the development of cardiology, to further scientific exchanges, and to help personal contacts of those working in this specialty."

Delegates at the Brussels meeting came from Belgium, Denmark, Finland, France, Great Britain, Greece, Holland, Italy, Yugoslavia, Norway, Portugal, Spain, Sweden, and Switzerland.

Provisional by-laws provide for a Council of seven and a Constitutive Committee represented by a delegate from each of the countries. It is proposed to hold a biennial congress at intervals between those of the Inter-American Society of Cardiology. Ultimate collaboration with the latter group is envisioned to form an International Cardiological Society embracing both hemispheres.

Officers chosen at the founding conference, all members of the Society's provisional Council, are: Professor Charles Laubry (France), Honorary President; Professor Gustav Nylin (Sweden), President; Dr. D. Evan Bedford (Great Britain); Professor Jean Lenégre (France) and Professor Eduardo Coehlo (Portugal), Vice-presidents; Dr. Francois van Dooren (Belgium), General Secretary; and Dr. Ivan Mahaim (Switzerland), Treasurer.

CORRECTION

In a previous announcement, it was stated that the meeting of the International Cardiological Congress would be held in Paris during the first week of July, 1950. This was incorrect. The meeting is to be held during the first week in September, 1950.

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